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HEMODIALYSIS IN CHILDREN

REPORT OF FIVE CASES

FRANK H. CARTER, JR., M.D.,* SHIGETO AOYAMA, M.D.,
ROBERT D. MERCER, M.D., AND WILLEM J. KOLFF, M.D.
CLEVELAND, OHIO

WITH the development of safer materials and techniques for hemodialysis, there has been a growing interest in the use of the artificial kidney as an adjunct in the management of uremia. Several types of artificial kidneys now are in use[1-4]; however, only a few reports have mentioned their use for the treatment of renal failure in children. Mateer and co-workers[5] described hemodialysis used in five children, and Merrill and associates[6] mentioned the use of the artificial kidney for a 3½-year-old child. This paper presents the findings in five children having renal failure treated with the artificial kidney and outlines other methods which have been helpful in management of that condition.

PRINCIPLE AND TECHNIQUE OF HEMODIALYSIS

In an artificial kidney, blood is circulated outside the body along a system of membranes. Through the membranes dialysis takes place, which means that small molecules go through the membranes while large molecules are retained. This has a dual effect: first, retention products, such as urea, creatinine, uric and metabolic acids, sulfates, and phosphates, are removed from the blood and, second, plasma electrolytes are adjusted through equilibration with the rinsing fluid.

Types of Artificial Kidneys Used.—The rotating type of artificial kidney[1] was used for only one patient (Case 1). The disposable coil kidney (Fig. 1)[4*] was utilized for the other four patients. The disposable coil kidney has proved to be an effective dialyzer that requires a minimum of time for preparation and is easily operated. Effective hemodialysis in children weighing less than 20 kilograms can be achieved with a single coil of the disposable kidney; in larger children both coils are used. To prime the single-coil system 400 ml. of blood is required, and 750 ml. to prime the twin-coil system.

From the Division of Research and the Department of Pediatrics, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute.

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*Present address: San Diego County General Hospital, San Diego, Calif.

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Rinsing Fluid Bath.—The composition of the rinsing fluid for the artificial kidney is given in Table I. The rinsing fluid is replaced every two hours to maintain a high gradient of retention products between the blood and the rinsing fluid. The amounts of sodium and potassium in the rinsing fluid can be varied. In severe hyperkalemia, potassium chloride is withheld from the first rinsing fluid to permit a greater reduction in serum levels. However, some potassium (2.5 meq. per liter) is added to the next baths to prevent depletion of the serum potassium to dangerously low levels.

Rate of Ultrafiltration.—With the disposable coil kidney, using two loops, the rate of ultrafiltration is 200 to 300 ml. per hour. When there is edema, it may be desirable to augment the rate of ultrafiltration. Resistance is offered to the flow of blood through the outflow tract by a screw clamp applied to the tract and adjusted until a pressure of 250 mm. Hg is obtained within the system. In this way 700 ml. of ultrafiltrate per hour may be removed.

Heparin.—Heparin, 1 mg. per kilogram of body weight, is administered to the patient at the onset, and 25 mg. is added for each 500 ml. of blood used in priming the apparatus or used for transfusion during dialysis. In addition, during the first four hours of dialysis, 5 to 10 mg. of heparin per hour is given. Clotting times are determined in Lee-White tubes; the first sign of clotting in the tubes is taken as the end point. The clotting time is maintained between 18 and 25 minutes.

Fig. 1.—The disposable coil of the artificial kidney and its container are shown in the rinsing fluid tank during hemodialysis. The patient's blood enters the coil through the two tubes leading to the inner part and leaves through the two tubes at the periphery of the coil. The rinsing fluid circulates up through and flows over the top of the coil and back into the tank.

Cannulization.—The most satisfactory source of blood for hemodialysis in children has been the inferior vena cava. A small incision is made over

the saphenous vein near its termination (fossa ovalis). The vein is exposed and ligated, and a large-caliber polyvinyl cannula is introduced and passed through the femoral vein into the vena cava. This cannula remains indwelling throughout the uremic phase and is used for subsequent hemodialyses, intravenous infusions, and for the collection of blood samples for laboratory determinations. During hemodialysis, blood is returned through a similar cannula in a vein of the arm. With this technique, blood-flow rates usually range from 200 to 400 ml. per minute.

status, repeatedly checks the cut-down sites to evaluate the extent of blood loss, if any, and continuously observes the extracorporeal system to ascertain the status of blood flow and of temperature, and whether there are blood leaks.

CASE REPORTS

CASE 1.—A 13-year-old boy was successfully operated upon for aortic stenosis by finger valvulotomy. During and after the operation he received 1,500 ml. of type B blood. He was later found to have type O, with very weak anti-B agglutinin titer. He developed shock and jaundice, and the urine became dark.

TABLE I. THE COMPOSITION OF THE RINSING FLUID

COMPONENT	AMOUNT (GM./100 L.)		(MEQ./L.) Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	HCO_3^-
Sodium chloride*	570	=	97	--	--	--	97	--
Sodium bicarbonate	300	=	36	--	--	--	--	36
Potassium chloride†	40	=	--	5	--	--	5	--
Calcium chloride	28	=	--	--	5	--	5	--
Magnesium chloride‡	15	=	--	--	--	3	3	--
Total			133	5	5	3	110	36

Invert sugar (Travert) 0.2 per cent.
Lactic acid to adjust pH to 7.4.
During dialysis 10 per cent CO_2 in O_2 bubbled through maintains the pH.

*When high serum sodium levels are present, 600 Gm. NaCl (138 meq. of Na^+) is used in the first bath, to prevent a rapid shift in serum sodium concentration.

†Twenty or 30 Gm. KCl (2.5 to 3.7 meq. of K^+) may be used, depending upon initial serum potassium levels.

‡When $MgCl_2 \cdot 6H_2O$ is used, 30 Gm. is required to provide 3 meq. per liter of Mg^{++} in the rinsing fluid.

Management of the Patient.—During dialysis management is directed toward allaying apprehension and pain and providing general comfort. A 2-year-old child who required sedation at the beginning of hemodialysis was given thiopental sodium rectally. Older children usually tolerated hemodialysis well with little or no sedation. Throughout dialysis, a nurse reports on and records blood pressure, pulse, and respiratory rate. The physician examines the heart and lungs frequently for changes in cardiac or respiratory

The urine cleared in a few days. He did not develop anuria although the urinary volume (400 to 900 ml.) was inadequate (Fig. 2). Blood urea rose to 240 mg. per 100 ml., serum potassium to 5.7 meq. per liter, and CO_2-combining power was 10 meq. per liter. On the eighth day, on the basis of progressive acidosis, uremia, and clinical deterioration, he was treated with the rotating type of artificial kidney[1] for four and one-half hours. One pint of low-titer type O blood was used to prime the artificial kidney. The run was uneventful and no reactions occurred. The urinary output on the day of dialysis was 1,400 ml., whereas

the previous day it had been only 890 ml. The day after dialysis the urinary output was 2,000 ml.; the boy had an uneventful recovery.

Comment.—If the boy's urinary output had continued to increase on the seventh day after the transfusion reaction, we might have postponed or even not have performed the dialysis. However, the output was slightly less on the sixth day, and the clinical condition was deteriorating. It is by no means implied that this patient would not have lived had he not been treated with the artificial kidney. However, his clinical management was greatly facilitated by the improvement that occurred the day after dialysis. It is impossible to predict the increase in urinary output in a patient with anuria. Even if diuresis increases rapidly, the uremic state will persist for a few more days. We believe that hemodialysis is indicated in order to bring about clinical improvement, so that further increase in urinary output may be confidently awaited without the likelihood that uremic complications will occur.

CASE 2.—A previously healthy 5-year-old girl developed acute glomerulonephritis with a convulsion, following otitis media. She first improved, as may be seen from Fig. 3; then oliguria and emesis recurred. Early in the fourth week convulsions also recurred. Blood pressure was 164/100 mm. Hg. Blood urea increased to 279 mg. per 100 ml. On the twenty-sixth day the patient was hemodialyzed for seven and one-half hours with the disposable single-coil (10-meter) kidney. Thirty-nine grams of urea were removed. Blood urea was reduced from 279 to 99 mg. per 100 ml. There was a marked and immediate improvement in sensorium. Nausea and vomiting disappeared. Hypertension came down without medication. Urinary output was decreased on the day of hemodialysis but was maintained above predialysis

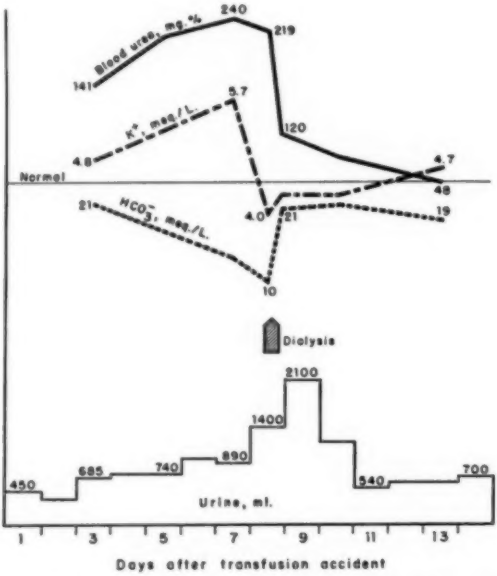

Fig. 2.—Chart of course in 13-year-old boy who had aortic valvulotomy, transfusion accident, and oliguria (no anuria) treated with rotating type of artificial kidney. Case 1.

levels on the following five days (Fig. 3).

Thereafter, urinary output progressively decreased to complete anuria. Renal function seemed hopelessly impaired and only supportive therapy was used. Increasing uremia, epistaxis, lethargy, recurring hypertension (170/120 mm. Hg), failing vision, congestive heart failure, pleural effusion, and convulsions led to the patient's death on the thirty-ninth day of her illness. Necropsy findings included chronic glomerulonephritis with devastating necrotizing renal arteriolitis similar to that seen in malignant hypertension.

Comment.—It is not clear why a condition that initially did not seem to differ from acute glomerulonephritis and even appeared to be on the way to recovery suddenly relapsed and became involved with necrotizing arteriolitis. The clinical improvement after one dialysis, as expected, included cessation of vomiting and clearing of sensorium. Blood pressure decreased and convulsions ceased. Whether the course would have been altered by earlier hemodialysis is open to speculation. There is nothing to suggest it.

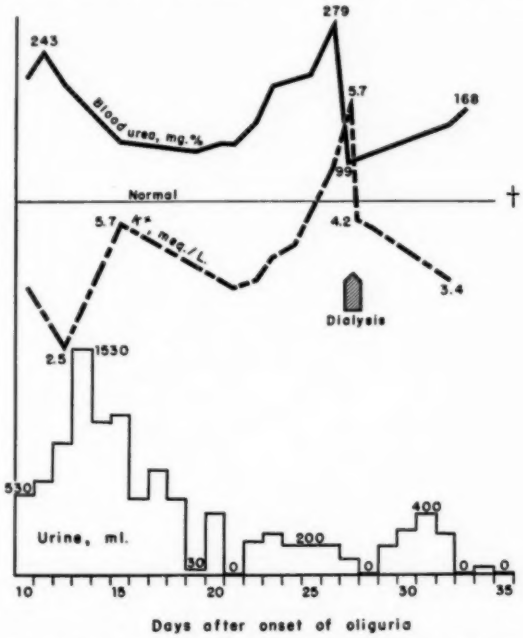

Fig. 3.—Chart of course in 5-year-old girl who had what appeared to be acute glomerulonephritis. Her condition improved temporarily after one treatment with the disposable coil kidney, but renal function was not restored. She proved to have chronic glomerulonephritis and necrotizing arteriolitis. Case 2.

CASE 3.—A boy, aged 2 years, was in good health until Aug. 14, 1956, when he developed a skin rash on the neck and groin, anasarca, and vomiting. Temperature ascended to 104° F. The patient passed small amounts of port-wine-colored urine, and then throughout the following three days became anuric. There was a history of two small, slow-healing sores on the skin two to three weeks prior to the present illness.

On the fifth anuric day he was brought to the Cleveland Clinic Hospital. Initial examination revealed a

well-developed, apprehensive, irritable, pale child with minimal generalized and palpebral edema. Blood pressure was 130/80 mm. Hg, pulse rate was 78, and respirations were 30 per minute. Laboratory findings were as follows: serum sodium 125, potassium 6, chloride 102, and CO_2-combining power 10.7 meq. per liter. Uric acid was 15.6 and blood urea 322 mg. per 100 ml. Hemoglobin was 10.5 grams per 100 ml. and the hematocrit reading 35 per cent. There was no urine available for examination. An electrocardiogram showed hyperkalemic changes.

On the day of admission the patient was given rectal thiopental sodium anesthesia and was dialyzed for five hours with a single-coil disposable kidney. Thirty-six grams of urea were removed. Blood urea was reduced from 324 to 93 mg. per 100 ml. (Fig. 4). General improvement was noted on the day after dialysis. Edema seemed less, and much of the central irritability was gone. He was maintained on 600 ml. of 10 per cent invert sugar in water given intravenously and 200 ml. of fluids and erythromycin given orally. Urinary output slowly increased, the diuretic phase beginning on the third postdialysis day. Albuminuria (trace to 1 plus) and microscopic hematuria persisted until the day of discharge. On the seventh postdialysis day he was inadvertently given a large solute load in the form of salted crackers, and generalized edema recurred. Edema was controlled by sodium restriction. The remainder of the hospitalization was uneventful. Six months after discharge he was reported to be well.

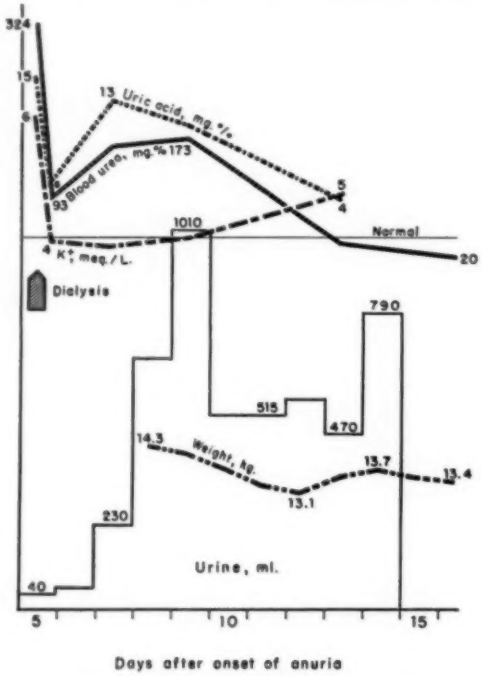

Fig. 4.—Chart of course in 2-year-old boy with acute glomerulonephritis, whose condition improved after one dialysis. Case 3.

Comment.—The diagnosis in this case is not certain. The condition

probably represented acute glomerulonephritis. In children, acute glomerulonephritis is not in itself an indication for hemodialysis; however, in the combination of rapidly progressing uremia, overhydration, acidosis, hyperkalemia, or clinical deterioration, hemodialysis may provide the time necessary for physiologic recovery.

This case report demonstrates the lack of a true diuretic phase, and the inability of the damaged kidney to adjust to an abnormal solute load.

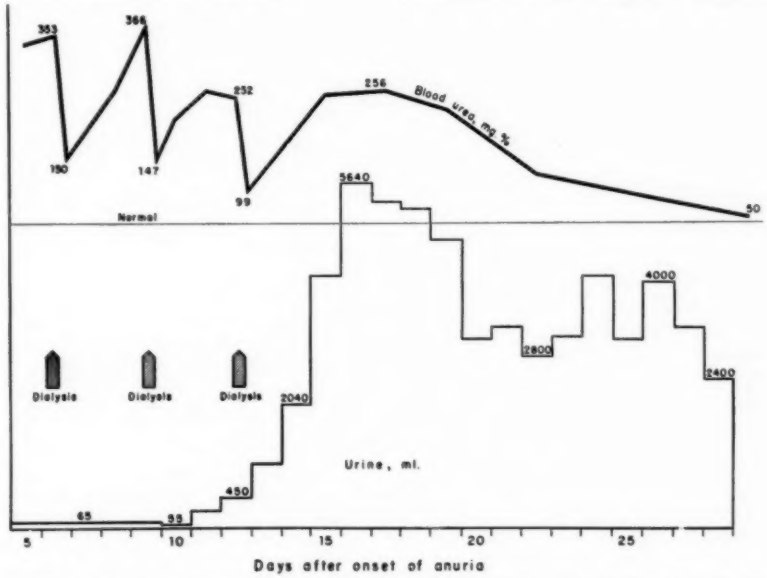

Fig. 5.—Chart of course in 14-year-old boy who had fulminating meningococcal sepsis, shock, and acute tubular necrosis. He recovered after three dialyses. Case 4.

CASE 4.—A boy, aged 14 years, developed fulminating meningococcal sepsis with multiple petechiae, ecchymosis, hematuria, and shock. He was treated with intravenous infusions, hydrocortisone, antibiotics, and pressor agents. The blood pressure was restored, but anuria (40 to 75 ml. urinary output per day) developed and persisted.

On the fifth anuric day the patient was transferred to the Cleveland Clinic Hospital. On entry the boy was critically ill but conscious. The blood pressure was 130/50 mm. Hg. Ulcers and encrustations were present on the lips, the tongue, and the oral and nasal mucous membranes. Stools were tarry. There was no evidence of overhydration. His fever had subsided, but to make sure that the sepsis was under control he was given 4 million units of sodium penicillin daily during the anuric phase. Sodium penicillin was used instead of potassium penicillin to avoid administration of potassium during anuria. Initial laboratory findings were serum sodium 131, potassium 4.7, chloride 87, and CO_2-combining power 18.9 meq. per liter. Urea was 340 mg. per 100 ml. On the sixth day, despite active bleeding from the stomach and from one kidney, the patient was hemodialyzed for four hours with the twin-coil disposable kidney. One hundred eight grams of urea were removed. Blood pressure and pulse rate remained stable throughout the procedure. Only 85 mg. of heparin was needed to maintain the clotting time between 16 and

20 minutes; there were no complications from heparinization and no increase of hemorrhage.

The patient improved during and following the dialysis. He was able to take fluids by mouth, and to move about in bed.

On the eighth anuric day he again became sleepy and appeared toxic. Urea was up to 261 mg. per 100 ml. He was redialyzed on the eighth and on the twelfth days (Fig. 5). During short periods of hypertension the boy became irritable and belligerent; after reduction of blood pressure his mental attitude improved. On the thirteenth day diuresis began; urinary output was 1,050 ml. and improvement was steady until his discharge twenty days later. Hydrocortisone was gradually withdrawn.

During the anuric phase, fluid management consisted predominantly of 40 per cent invert sugar in water infused through an indwelling plastic cannula inserted through the saphenous vein into the inferior vena cava. This cannula functioned for fifteen days, and also was used for all three dialyses.

Comment.—When the sepsis had become controlled with antibiotics and the adrenal insufficiency (if present) with hydrocortisone, the results of shock and toxic damage became evident in the form of acute tubular necrosis and anuria.

In the case of crush injury or severe infection, as seen here, early and frequent hemodialyses are mandatory to reverse rapidly progressing uremia, acidosis, and hyperkalemia that otherwise will lead to sudden death.

The third hemodialysis was undertaken at a time when the patient was remarkably improved and the diuretic phase appeared imminent. This procedure reflects our present attitude (see Case 1). When a patient is bleeding we must weigh the risks of heparinization; currently our experience is encouraging. Three or four extra units of fresh blood is made available for immediate use, and the amount of heparin used is less than usual.

The administration of 40 per cent invert sugar into the vena cava through a large indwelling cannula has ensured a high caloric intake.

CASE 5.—A boy, aged 9 years, developed what appeared to be acute glomerulonephritis following an acute infection of the upper respiratory tract. A few milliliters of urine obtained for analysis showed 1 plus albumin and abundant red blood cells. He became anuric and on the seventh anuric day was admitted to the Cleveland Clinic Hospital.

Physical examination on entry revealed a well-developed, lethargic boy with generalized edema. Blood pressure was 130/85 mm. Hg, pulse rate was 90, and respirations were 34 per minute; temperature was 98.6° F. The lungs were clear. An electrocardiogram demonstrated early hyperkalemic changes. Initial laboratory findings were hemoglobin 11.7 grams per 100 ml., blood urea 240 mg. per 100 ml., serum sodium 117, potassium 6.9, and CO_2-combining power 7 meq. per liter.

The patient was given an intravenous infusion of 500 ml. of 10 per cent invert sugar in water that contained 120 meq. of sodium lactate, 4 Gm. of calcium gluconate, and 500 mg. of erythromycin to curb the danger of acute potassium intoxication. The following morning, the eighth anuric day, there were some improvement in respiration and diminution in lethargy, but the child remained critically ill. He was dialyzed with the twin-coil disposable kidney for four hours (Fig. 6). Sixty-six grams of urea were removed. Blood urea decreased to 84 mg. per 100 ml., serum potassium to 4.2 meq. per liter, and the CO_2-combining power increased to 22.3 meq. per liter. At the end of the hemodialysis, the child was moderately alert and demanded something to eat. A three-pound loss in weight occurred,

with a notable reduction in the generalized edema. Transient hypertension (160/90 mm. Hg) developed during the hemodialysis but was controlled with small doses of pentolinium bitartrate.

The boy remained anuric throughout the next two days but continued to be hungry and appeared clinically improved. On the eleventh anuric day he became drowsy, febrile, and had a rise in blood pressure (170/90 mm. Hg). Edema was more pronounced. Again he was treated with the twin-coil disposable kidney, this time for tachycardia. He was transfused with 300 ml. of packed red blood cells. The following day the blood pressure rose to 220/120 mm. Hg, and a generalized convulsion began, which could not be controlled by sedative and ganglion-blocking drugs. An intravenous infusion of sodium nitroprusside[7] brought about a rapid return of the blood pressure to 120/70 mm. Hg, and the immediate cessation of convulsions. The infusion was continued with decreasing concentrations of nitroprusside over the next twelve hours without alteration in the blood pressure.

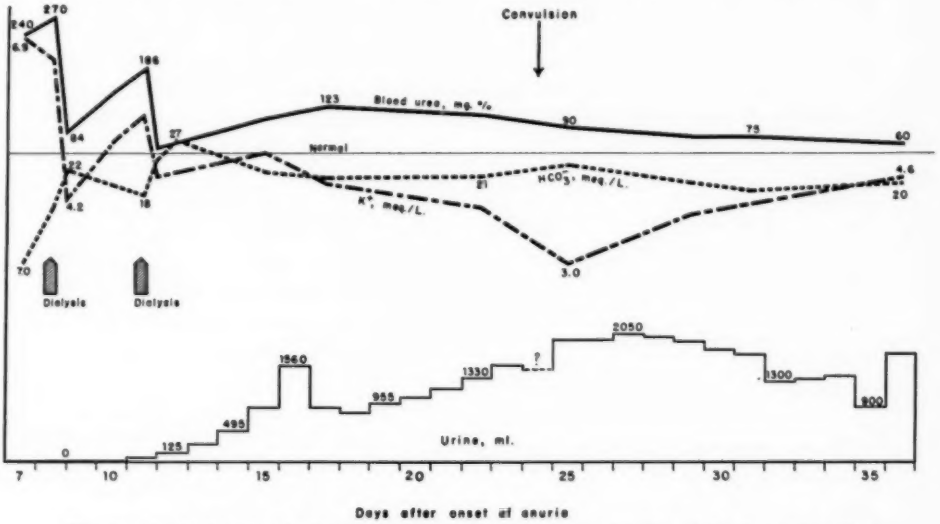

Fig. 6.—Chart of course in 9-year-old boy with what appeared to be acute glomerulonephritis. His condition improved after two dialyses. Later he developed acute hypertension and convulsions. When he was discharged from the hospital, his condition had improved but he had slight hematuria. Case 5.

five hours. On the twelfth day urinary output began with 125 ml. and on the sixteenth day had increased to 1,560 ml.

On the thirteenth day hypertension recurred, and continued throughout the next twelve days. Increasing doses of antipressor drugs were required to maintain the blood pressure at 150/90 mm. Hg. On the twenty-fourth day the hemoglobin was only 5.6 grams per 100 ml. It was believed that this anemia contributed to his dyspnea and The child received no further antipressor medication. He remained normotensive (120/70 mm. Hg) throughout the remainder of his stay in the hospital.

Following the convulsion the urine became grossly clear and the urinary output increased up to 2,000 ml. per day. The child continued to improve, and went home with slight residual hematuria.

Comment.—This boy, upon initial examination, was in a fairly severe

uremic state. To reverse the acidosis and to prevent the further development of hyperkalemia and its effects, he was given intravenously a combination of invert sugar, sodium lactate, and calcium gluconate. As anticipated, there was transient improvement, a respite that allowed preparation of the artificial kidney.

A refractory convulsive state secondary to renal failure sometimes can be controlled by hemodialysis. In this instance, however, the convulsions were secondary to hypertension and were controlled only when the blood pressure was reduced. The intravenous use of sodium nitroprusside was lifesaving. Although the patient was discharged from the hospital in a normotensive state, a guarded prognosis must be made as to the ultimate outcome.

DISCUSSION

General management of the uremic child is directed toward (1) establishment of fluid balance, (2) vigilance over the status of electrolytes, (3) maintenance of maximum caloric intake in the hope of reducing undue breakdown of protein and formation of retention products, and (4) prevention of infection. Dialysis, finally, is the most powerful means of overcoming and correcting the shortcomings of the conservative attempts.

1. *Fluid Balance.*—During the anuric phase 20 to 30 ml. fluid intake per kilogram of body weight per day was sufficient to maintain fluid balance in our five cases. In normal children without fever the rate of insensible loss of water is about 500 ml. per square meter of body surface per day, but in anuric or edematous children we believe that it is less. Losses by sweating, vomiting, diarrhea, and by that small amount of urine that is produced should be considered. The best general guide is the daily weight of the patient. So long as a child is able to take something by mouth, intravenous administration of fluid should be avoided. During the early diuretic phase, the fluid lost must be replaced, but after the peak of diuresis has been reached careful curtailment of fluid intake should be undertaken, to prevent a prolongation of diuresis simply due to water loading.

Rarely Need Transfusion: Progressive anemia consistently follows the course of uremia. Hematocrit levels usually become stable between 25 and 30 mm. Generally the anemia is well tolerated, and attempts to restore hematocrit levels to normal are quite useless and even dangerous. Following transfusion there is a temporary rise in blood hemoglobin and then a decrease to pretransfusion levels. The addition of blood to an already expanded intravascular compartment invites hypertension, congestive cardiac failure with pulmonary edema, and convulsions. When transfusion is unavoidable, multiple small infusions or, rather, exsanguinotransfusions (replacements) are better than one large transfusion.

2. *Vigilance Over Status of Electrolytes.*—Correction of electrolytes to a supposedly normal level is not our aim and may even be dangerous. We change electrolytes as little as possible.

During the anuric phase no sodium is given in any form unless it has been demonstrably lost in large quantities or a low alkali reserve (lower than 15 meq. per liter) induces us to give sodium lactate (or sodium bicarbonate), 10 to 40 meq. per day. It rarely is necessary to give sodium chloride, since retained metabolic acids, such as $SO_4^=$,

will replace Cl^-. Potassium salts rarely need be given.

During the diuretic phase sodium chloride sometimes must be provided. Two and one-half grams per liter of urinary output is only a rough guide, as it may be too much. In this phase potassium salts may have to be provided. (One glass of orange juice contains 20 meq. of potassium.) Hypocalcemia, although often present, rarely produces the symptoms of twitching and convulsions erroneously attributed to it.

3. *Caloric Intake.*—By providing maximal daily caloric intake we try to encourage anabolic processes, diminish wasting of body protein, slow down the formation of retention products, and retard derangement of electrolytes. Caloric supplements in the form of fat emulsions, hard candy, and ginger ale help to boost the daily caloric intake.

When anorexia precludes adequate oral intake and intestinal peristalsis still is present, occasionally a fluid homogenate delivered as a constant drip through a small plastic gastric tube will maintain nutrition.

The administration of 40 per cent invert sugar provides a large caloric intake in a small volume and has produced no demonstrable local or hemolytic effects when introduced into the vena cava.

4. *Prevention of Infections.*—The uremic child is extremely susceptible to infection. In addition to the danger produced by infection itself, the septic state increases catabolism which, in turn, increases the uremia. Adequate nursing care with particular emphasis on general bed care and oral hygiene is essential. Frequent physical examination for the early detection of septic foci must be made. Surgical care of cut-down sites minimizes complication from this source. In addition, it has been our practice to give erythromycin prophylactically throughout the period of danger.

Indications for Dialysis.—In severe uremia, a state is reached where conservative procedures become inadequate. With progression of the uremic process there begins a vicious cycle. Physical degeneration adds pathologic changes to an already delicate therapeutic problem. Vomiting, for example, makes caloric intake difficult and disturbs electrolyte balance. Coma prevents expectoration and promotes pulmonary infection. Insufficient caloric intake, electrolyte disturbance, and infection all enhance the uremia. We believe that dialysis should be undertaken before the patient enters the cycle.

Indication for dialysis is both chemical and clinical. Chemical indications are a CO_2-combining power of less than 12 meq. per liter, a blood urea level of more than 200 mg. per 100 ml., and chemical and electrocardiographic evidence of hyperkalemia (usually a serum potassium level of more than 6.5 meq. per liter).

Two clinical patterns of behavior should be a forewarning to the approach of more serious uremic complications. In the first there are lethargy, apathy, and somnolence. In the second there are irritability, restlessness, and psychosis. Either of these patterns frequently is associated with anorexia, nausea and vomiting, and alteration in cardiovascular status, especially with wide fluctuations in blood pressure.

Early and frequent hemodialyses promote an improvement in sensorium, a return to the feeling of well-being, and a return of appetite. Catabolic retention products are reduced, a relative restoration of electrolyte equilibrium is obtained, and the total amount of body water is lessened. In all five patients here discussed clinical improvement after hemodialysis was evident and clinical management became easier.

It must be stated that each hemodialysis is undertaken at a calculated risk, but the risk is small. The fear of hemorrhage has hampered the application of hemodialysis, but, in general, uremic bleeding, such as ecchymoses and bleeding from the gums or from the gastrointestinal tract, lessens after hemodialysis. Bleeding from wounds or ulcers must be evaluated for the individual patient. In the patient with meningococcemia there was a slight, transient increase in gastrointestinal and in genitourinary bleeding, but it was not serious. On occasion, hemodialysis has been maintained on as little heparin as was required for the blood used to prime the artificial kidney. Sudden changes in blood pressure might constitute a serious risk: an increase in blood pressure could lead to convulsions; a decrease, to sudden death. No alarming changes happened in the eight dialyses here discussed; but if they had occurred they would have been amenable to treatment. In the hands of a well-trained team, hemodialysis is not only helpful in producing a smoother course in these children, but it may also be lifesaving.

SUMMARY

Eight hemodialyses were performed in five patients whose ages ranged from 2 to 14 years. Four patients survived; one patient improved temporarily and then died. The etiologic factors that lead to renal failure were transfusion accident in one patient, shock secondary to meningococcal septicemia in one, chronic glomerulonephritis with necrotizing arteriolitis in one (the patient who died), and what appeared to be acute glomerulonephritis in two patients.

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THE SOCIAL MANAGEMENT OF THE EPILEPTIC CHILD AND HIS PARENTS

SAMUEL LIVINGSTON, M.D.
BALTIMORE, MD.

THE primary purpose in the therapy of any disability is the rehabilitation of the patient to a life as nearly normal as possible within the limitations of the disability. In epilepsy the efforts to control the seizures are, of course, of primary importance. But whether full control is achieved or whether recurrent seizures persist, there remain many problems concerning the psychological management of the patient and his parents and their relationship to the social milieu in which they live. The conditions which surround each case are so varied that only general advice can be offered. Principles and methods which we have found to be effective will be discussed, but it should be realized that no set of rules can be applied indiscriminately to each case. The application of these principles also depends on the basic attitude of the doctor to the disorder of epilepsy.

It appears that some physicians still have the impression that epilepsy is the most serious of the convulsive disorders and also that it is a hopeless and intractable condition. This attitude was reflected by a general practitioner who recently was seen as a patient in our clinic. At the start of the interview this physician said: "I certainly hope I do not have epilepsy." We were unable to establish a cause for his convulsions. We, therefore, told him that our diagnosis was a convulsive disorder of undetermined etiology (or epilepsy). We explained to him that his disorder would in all probability be much more serious if we had been able to discover a cause. After thinking the matter over for a moment or so, he agreed. As he left the consultation room, he said: "Gee, I certainly am glad I only have epilepsy." This attitude is extreme, but illustrative.

From the Department of Pediatrics, Johns Hopkins University School of Medicine, and the Epilepsy Clinic, Johns Hopkins Hospital.

THE ATTITUDE OF THE PARENTS TO EPILEPSY

The first reaction of parents to a diagnosis of epilepsy in their child is one of horror and frequently of disbelief. This is a moment requiring tact and sympathetic understanding. The general idea that epilepsy is a shameful disease—a stigma—is often foremost in the minds of the parents. Several points should be clearly emphasized. First, the parents should be emphatically told that there is no reason why epilepsy should carry a stigma; and, second, that it is a disorder differing in no way in its social implications from rheumatic fever, tuberculosis, or diabetes.

Some physicians have adopted the policy of "hiding" the word epilepsy from the parents of epileptic children.

Clinics have been established throughout the country dealing with convulsive patients and terms such as "convulsive clinics" or "seizure clinics" have been assigned instead of the term epilepsy clinic. In several instances when we asked why these latter terms were employed instead of the term epilepsy clinic, we received the following answer: "I do not wish to 'stigmatize' our clinic with the term epilepsy."

We do not believe that it is wise that the term epilepsy be kept from the parents. I would like to cite the following case as an example. The mother of one of our patients stated that she took her child who had suffered with several convulsions to a physician. After a thorough examination the physician told the mother that he was unable to demonstrate a cause for her child's convulsions. The mother then asked the doctor the question: "Does my child have epilepsy?" The physician in turn answered "Mother, I do not know what the word epilepsy means. In fact, the term epilepsy does not exist in my dictionary. So far as I am concerned your child suffers with convulsions of undetermined cause." The mother left this doctor's office quite confused. She was made more confused when her neighbor, who knew that the child had suffered with convulsions, asked whether she thought the child had epilepsy.

The mother remembered from the interview that her doctor had said there was no such disorder as epilepsy and that the word epilepsy did not exist in his dictionary. When she was able to find the word in Webster's dictionary, as well as in several textbooks from the library, she became more upset. She then called her doctor and told him that he confused her, that she did not have any confidence in his diagnosis, and also that she did not think his dictionary was a very important one because the term epilepsy was in Webster's dictionary and in books by many famous doctors.

We do not believe that one can "hide" the word epilepsy from the parents. The term is used in medical textbooks, is seen by the public in newspapers and magazines, and is heard on radio and television broadcasts. We believe that it is best to face this problem honestly. We explain first that the term epilepsy is derived from the Greek "Epilepsia" which, when translated into English, means "seizure." We also tell them that the term epilepsy is assigned to those patients who suffer with convulsions or seizures and in whom a definite cause cannot be established.

Many parents and some doctors are under the impression that epilepsy is a most serious disease with a hopeless prognosis. We console our patients to some degree by explaining that the causes of seizures in children are many, giving as examples brain tumors, hypoglycemia, and hypocalcemia. We tell them that generally convulsions of undetermined cause (epilepsy) are of much less serious nature than these disorders in which a cause for the convulsions can be found.

Many parents become confused when you tell them that you are unable to find a cause for their child's convulsions. Generally they want the reassurance that comes when they believe that the doctor understands the case, since they feel that if he does not know the "cause" he cannot help them. We explain that it is fortunate that

we were unable to demonstrate a cause for their child's convulsions because if we had been, the condition would probably be much more serious. For example, it is much more difficult, in most instances, to control the seizures associated with hypoglycemia or hypocalcemia, and obviously convulsions associated with brain tumors are always very serious. We also tell the parents that today, with the newer techniques and a better understanding of the treatment of epilepsy, approximately 80 per cent of children can have their seizures satisfactorily controlled by proper medication, and many will even be able to stop taking drugs later on.

Many people have the impression that there is a definite relationship between mental retardation, and even insanity, and epilepsy. We inform the parents that this impression is definitely unwarranted and that it stems from the time when there was no effective remedy for seizures. Epilepsy was then regarded as a hopelessly incurable condition. For this reason many patients with epilepsy were placed in institutions which housed mentally defective patients, idiots, and also other patients with many serious mental illnesses. One might as well believe in a relationship between genius and epilepsy as between mental retardation and epilepsy. Among the great men of history who are reported to have had epileptic seizures are Buddha, Socrates, Alexander the Great, Julius Caesar, Mohammed, Peter the Great, and Napoleon Bonaparte. Actually there is no consistent relationship between epilepsy and either mental retardation or genius. An epileptic may possess other infirmities or he may be richly endowed.

One gets a much better over-all result when the parents are educated in regard to the general plan of therapy for epilepsy. We encourage the parents who are intelligent enough to read and understand to study up on the condition of epilepsy and to learn about the various drugs which are now used in the treatment of epilepsy. The parents should be told that there are many drugs which are available for the control of epileptic seizures and that it may be necessary to give each of these a fair trial in order to find a proper drug or drugs for their child. We tell the parents that we usually begin treatment with one drug and that the dosage of this drug may have to be changed and other drugs may have to be tried before the proper medication is found for their child.

It has been our experience that when the general plan of treatment is explained to the parents, they do not become discouraged too quickly. We often compare the treatment of epilepsy with the treatment of diabetes. We tell the parents that when a patient suffering with diabetes comes to a doctor, he determines the blood sugar level and at first gives a little bit of insulin. Later he determines the blood sugar level again and if the amount of insulin which he gave initially did not return the blood sugar to normal then he has to give a little bit more. We find that when the treatment is explained at the onset in this manner, the physician gains the cooperation and confidence of the parents.

The parents must be reassured that nothing they have done or not done has contributed to the development of the epilepsy. This is important! We

have found that frequently parents believe that the condition has resulted from some error of omission or commission on their part. In many cases the development of epilepsy in a child is considered "punishment for their sins." Such guilt feelings are seldom expressed openly, and indeed may come from deep in their subconscious minds. Nevertheless, they affect the parents' attitude toward the child.

Such feelings may seriously impede the physician's efforts to establish a wholesome family relationship. We often find that reassurance and support must be continued throughout the course of treatment.

THE ATTITUDE OF THE PARENTS TO THE CHILD

The parents should be convinced that their efforts should be directed toward raising a "normal child" within the limits of the disability. Too frequently an epileptic child in a family is treated as "something special" and allowed to do as he pleases, pampered and overprotected by his parents. Unreasonable demands are granted because of a mixed emotion that this is a poor unfortunate child who should be given the greatest possible happiness, and that an emotional upset might precipitate a seizure. Most parents have the impression that if the seizures are aggravated by circumstances which "excite" the child, he should be made to live in as quiet and sheltered a manner as possible. Within limits there may be justification for such a stand, but in the majority of cases such failure of authority to set reasonable limits carries the more serious risk of establishing a lifelong neurosis based on lack of security, and the concomitant feelings of antagonism, resentment, and inferiority.

In many cases parents of a child who has had only an occasional epileptic seizure consider him ill in the same respect as if he were afflicted with active tuberculosis or acute rheumatic fever. Such a child is encouraged and, in many instances, forced to rest and take daily naps. Such attitudes should be discouraged. The parents should be instructed to allow their children to play and conduct themselves, if possible, in the same manner as their normal associates. Physical activity, contrary to the layman's belief, favorably affects an epileptic disorder in most instances. It is generally known that epileptic patients have fewer seizures when they are participating in the general physical activity of the normal child, such as playing football, baseball, or other outdoor games. It has also been shown that abnormalities in the electroencephalogram of epileptic children frequently become more numerous during the resting state.

Children have often been referred to us by physicians who have made a diagnosis of epilepsy and have told the parents that the child should not be allowed to swim, ride a bicycle, play baseball, or participate in any of the activities usual for his age group. Even though a child may have an occasional convulsion, there is no valid reason for such an edict. There is always a certain hazard in life for everyone, we tell the parents, and in some instances this may be greater for the epileptic child. But the disadvantage of the increased hazard, if it is a reasonable one, is offset by the advantage of a normal life. Certainly there

is no reason to prohibit swimming for the child who suffers with occasional seizures. To be sure, no child should be allowed to swim unless there are adequate facilities to rescue him if trouble develops. The same safety rules which will protect a normal child who develops "cramps" will protect an epileptic child who has a seizure while in the water. The slightly increased hazard of bicycle riding for the epileptic having infrequent convulsions is only for traffic; this problem must be adjusted to the individual patient. A convulsion which arises on a baseball field is no more hazardous than one occurring in the home. We recommend only two major restrictions for children who have seizures: (1) they should not be allowed to climb into positions from which a fall would be dangerous and (2) swimming should be supervised by adults. We explain to the parents that there is a certain small, calculated risk when they allow their child to participate freely in all normal childhood activities. However, they must weigh this against the greater risk of instilling inferior attitudes which would handicap the child more severely and more surely than the convulsions. "Invalidism" in adult life does not depend on the extent of a physical disability—it is a state of mind.

The privilege of driving a motor vehicle is important. Denial of the driving privilege deprives a person of work that requires the occasional use of an automobile or of jobs located where the automobile is the only feasible transportation. Denial of this privilege to controlled epilepties creates a serious obstacle to their rehabilitation.

It is obvious that an indiviual who has seizures should not drive a motor vehicle. However, there is no valid reason why a controlled epileptic who is physically and mentally capable of driving should be denied this privilege. We have not encountered a single accident, attributable to a seizure, in hundreds of our controlled epilepties who have been driving automobiles for years.

The laws governing motor vehicle drivers' licenses vary from state to state. They may be found in *Epilepsy and the Law* by R. L. Barrow and H. D. Fabing.*

THE RELATIONSHIP OF THE PATIENT TO HIS DISABILITY

Parents frequently ask the doctor the following question: "What and how much should I tell my child about his illness? They will invariably say: "I certainly do not want to tell him that he has epilepsy. I do not even want to mention the word epilepsy to him."

From the standpoint of the patient, the implications of his handicap should not be minimized. The instructions given in each case must be individualized, depending upon the patient's likelihood of understanding the situation.

We usually tell the young child that he has some sort of disturbance, such as fainting spells or the like. Occassionally we use the term convulsion. We tell him that it is important he take medicine every day to prevent the spells from "coming back," so that he can "do everything that he wants to." As the child grows older he should be acquainted with the responsibilities his

*Hoeber-Harper Publishers, New York, 1956.

condition imposes. Generally, by the time he has reached 18 years of age he can be given a full account.

We believe that, in most instances, it is best not to tell the younger child about epilepsy. This is true because he may tell his playmates. They in turn may tell their parents about little Johnny who has epilepsy. Other parents may not understand this condition themselves and prohibit their child from playing with the epileptic child. The parents of several of our patients have informed us of such situations.

Young children sometimes are thoughtless and "cruel." The following is an example. A young boy learned that one of his classmates had epilepsy. During recess on the playground, in the presence of the epileptic child, he shouted: "Don't play with Johnny because he has epilepsy" and "Johnny has epilepsy and this is very bad." He later told the school principal that his parents told him that all epilepties are "dumb and crazy."

When a child has been subjected to and disturbed by such ridicule, the parents should explain to him as simply as possible the meaning of the word epilepsy. We frequently tell our younger patients that the word epilepsy is a "foreign" word or "Greek" word which in "English" means "fainting" or convulsion. We also tell them that some people do not understand the meaning of the word and think that it has a "bad meaning," but it does not. The childhood expression "Sticks and stones can break your bones, but names can never hurt you" has also been helpful in some instances.

If a child is already accepted by other children, the commotion soon dies away. However, if he is a newcomer to the group, unpopular, or in any other way an "outsider," this attitude of other children can become an almost insuperable obstacle to a child.

Younger children generally sense any type of restraint and soon learn that they are not normal. Even at younger ages when they cannot understand the reasons for the handicap, their ego and pride can be enhanced by activities in which they can excel. Hobbies are to be encouraged but not forced. A skill in photography or music or model building can be a real substitute for failure to compete physically with playmates. In those moments when life seems dark because of such failures, praise for other accomplishments is often of great value in building morale. The emphasis should never be on "you can't do this" but rather "you can do this."

THE RELATIONSHIP OF THE PATIENT AND THE PARENTS TO THE COMMUNITY

Despite the most skillful handling of the individual problems of the epileptic patient, there will be other problems which arise from the attitude of an ill-informed population. Since biblical days, epilepsy has carried with it the idea of uncleanliness, ungodliness, and even of insanity. Even today some parents warn their children to stay away from a schoolmate who has epilepsy because "he has fits," "he is crazy," etc. Even when such advice is prompted only by the desire to spare the young child the unpleasant sight of a seizure, it creates problems for the patient. For the present, the epileptic child and his parents will have to accept this community attitude. Such adverse attitudes are more prominent in small towns than in larger cities. This is due to the closer

contact of individuals within a small community. Some of our patients living in smaller communities have been completely isolated from normal companionship and also have had extreme difficulty in obtaining work. This attitude persists even if the patient remains free of seizures for many years. Some of our patients' parents have found it necessary to leave communities in which they had lived for years and had enjoyed good reputations and good jobs, because of such difficulties with their children. In one small town a woman saw a mentally retarded child have a seizure on the street. Because this child was mentally retarded she spread a rumor throughout the community that all epilepties are mentally retarded. As physicians it is our duty to dispel these misconceptions at every opportunity. Much is being done today in this respect and it is to be expected that in a few more years the public attitude toward epilepsy may have become more realistic.

A frequent question which is asked us by parents is, "Shall I tell the teacher or the school authorities that my child suffers with epilepsy?"

We have been informed by some parents that other physicians have advised them not to mention the word epilepsy to the schoolteacher or school authorities but merely to tell them that the child suffers with convulsions or seizures. We believe that this is futile since today most of the school authorities and teachers are familiar with epilepsy as a disorder characterized by "seizures" or "convulsions," although some of them do not realize the exact nature of the disease.

As with all types of treatments and also all types of general advice, each case must be individualized. Generally, however, we believe that in the case of a young child who suffers with infrequent seizures and who has never had a spell at school, it is best not to mention the disorder in any manner to the schoolteacher or school authorities. This is particularly true in those instances where the seizures have only occurred at night during sleep. It is quite possible that such children would never have an attack at school.

While this course may seem morally wrong, we justify it by considering the adverse effects such knowledge might produce. Since many teachers or principals do not themselves completely understand the condition of epilepsy, they may treat the child in a manner which sets him apart from other children. We have found in some instances that even when a teacher apparently understood the condition, she overprotected the child and looked upon him as someone different from the other children. Every time the child did something which appeared to be "out of order," the teacher attributed it to the epilepsy. Many of the teachers were in a constant "state of tension" for fear that the child might have a seizure in class. Obviously this is not good for a child.

However, if a patient suffers with frequent seizures or manifests side reactions, such as drowsiness from drug therapy, it is best that the school authorities be told about the condition in detail.

Older patients, in the higher schools, should have the condition explained to them. When the patient has a good understanding of the disorder then it is in order to inform the school authorities of the condition. For the good of the child they should know

the actual situation, and with the consent of the parents this appraisal should be submitted by the physician. He should state honestly that the child is an epileptic and just as honestly what frequency of convulsions might be expected. It may take some persuasion to convince a principal that no material upset in school routine will result if the child should have an occasional seizure.

Mentally retarded children and those who have frequent seizures ordinarily should not be sent to regular public schools. This is a field for special classes.

TRAINING FOR THE FUTURE

During childhood, plans are laid for the adult future. Boys must acquire the training and education which is needed for a remunerative occupation. Girls generally need to acquire the many skills needed to manage a household.

It is the responsibility of the physician to see that advice on these matters is forthcoming. It is obvious that an epileptic should not aspire to become an air pilot, steeplejack or a deep-sea diver. But outside of the exotic vocations there is little that an epileptic cannot do. Many gifted men have been epileptics.

The only criterion which must be considered is whether the frequency of attacks would jeopardize the patient or his chances for advancement. The problem of mental retardation, if this is present, should be handled in the same manner as it would be for mentally retarded children who are not subject to seizures.

MARRIAGE

Just as the problem of an adult occupation is important with boys, with both boys and girls there is the question, "Can I marry?" and "Is it reasonable to have children?" Certainly there is no reason for the epileptic not to marry. The emotional satisfaction of a home of his own has helped stabilize more than one patient. Of paramount and obvious importance, however, is the necessity that the prospective marital partner be fully aware of the situation. Physicians can do much by inviting both partners for a consultation in which all questions can be answered to the best of his ability.

The following question is natural, "What about our children?" In our present state of knowledge this is difficult to answer because no exact information is available. In dealing with the problem of inheritance with couples contemplating marriage, it is better to present the facts and leave to them the decision concerning the advisability of having children. This is a personal problem; some individuals would prefer a calculated risk rather than be denied the satisfaction of parenthood. They can be told that the odds quoted in the literature with regard to the chances of an epileptic having an epileptic child varies all the way from 1:10 to 1:100, the average being about 1 to 25. We base our decision primarily on the frequency of the patient's seizures and his physical and mental ability to raise a family. Obviously an individual who has frequent epileptic seizures would be unable to care for a family. We also tell the individuals that with the development of the newer medical and surgical techniques for the control of seizures, the outlook for those afflicted with recurrent seizures is being steadily improved.

PATIENTS REQUIRING INSTITUTIONAL CARE

The group of epileptic patients who cannot be cared for at home and who require institutional care are in general those who are having frequent seizures. These patients are also almost invariably mentally retarded. The basic problem is, therefore, more the case of the mentally retarded child than the epileptic. For such children institutional care is usually the only recourse. Most parents hesitate to take such a drastic step. It must be carefully explained that the child will not suffer; that his mentality is so low that he will quickly be as happy in the institution as at home; that even if the institution is crowded beyond what the parents might wish, the patient lacks aesthetic sense and will not suffer; and, finally, that a young couple should not sacrifice themselves, their other children, or their financial future in a misguided emotional effort to do everything for a hopeless child.

In conclusion, it should be reiterated that although certain basic principles may be discussed, the problem is different in each individual case. The physician can arrive at no better conclusion than by asking himself, "What would I do if this were my child?" and advising the parents accordingly. There is no substitute for a calm realistic attitude which accepts each patient as a person with a certain degree of handicap, but with certain potentialities which are to be encouraged to the utmost. The doctor's attitude will be reflected in the ability of the parents and friends to accept the patient as an individual rather than as a stereotyped "epileptic." Failure in this respect means failure in the rehabilitation of the patient.

For chin-cough or hooping cough. Rub the feet thoroughly with hogs lard, before the fire, at going to bed, and keep the child warm therein,
Or rub the back at lying down with old rum. It seldom fails.

BICKERSTAFF'S BOSTON ALMANACK FOR 1769.

GENERALIZED CYTOMEGALIC INCLUSION DISEASE

ARTHUR E. MCELFRESH, M.D., AND JAMES B. AREY, M.D.
PHILADELPHIA, PA.

ALTHOUGH the inclusion-bearing cells which characterize cytomegalic inclusion disease were reported as early as 1904 by Jesionek and Kiolemenoglou[1] and by Ribbert,[2] it is only in more recent years that the disease has been recognized as a clinical as well as a pathologic entity. In an excellent review of the literature Smith and Vellios[3] reviewed the records of sixty-nine instances of cytomegalic inclusion disease reported up to 1950, to which they added twenty additional cases. In the same year Wyatt and associates[4] suggested the possibility of ante-mortem diagnosis of cytomegalic inclusion disease by exfoliative cytologic studies of the urine. It was not until 1952, however, that Fetterman[5] and, later, Mercer and associates,[6] recorded the first ante-mortem diagnoses of this disease by demonstrating the characteristic inclusion-bearing cells in urinary sediment. Gallager[7] in 1952 reported the findings in an infant with cytomegalic inclusion disease in whom the diagnosis was established by histologic examination of pulmonary tissue which had been resected because of the presence of multiple cysts. The clinical manifestations in this infant were predominantly respiratory in nature with only limited evidence of systemic involvement. Resection of the cystic segments of the right lung, in which the inclusion-bearing cells were identified, was followed by complete recovery of the infant, who subsequently developed normally. No mention was made of the presence or absence of inclusion bodies in the urine of this patient. Margileth[8] in 1955 reported the first instance of survival of an infant in whom the diagnosis of cytomegalic inclusion disease was made by examination of smears of the urinary sediment. The infant, who was 22 months of age at the time of the report, has rather severe mental retardation; cerebral damage may have resulted from the cytomegalic inclusion disease per se, from kernicterus, or from an intracranial hemorrhage. Subsequently Bratenahl[9] has observed one other infant with cytomegalic inclusion disease who is living, with evidence of cerebral damage, at the age of 1 year. Birdsong and colleagues[10] have reported an infant who is living and well, with no evidence of mental retardation, at 10 months of age. Icterus, bleeding phenomena, and hepatosplenomegaly were present at birth, at which time inclusion-bearing cells were demonstrable in the urine. Finally, Smith[11] in 1956 and Weller and co-workers[12] in 1957 reported the isolation of the virus responsible for the disease.

From St. Christopher's Hospital for Children and the Departments of Pediatrics and Pathology, Temple University School of Medicine.

Thus, within the past five years cytomegalic inclusion disease has assumed clinical importance as a disease of neonatal life and can no longer be considered of interest to the pathologist alone. Moreover, with improved diagnostic methods it is becoming apparent that the disease is not uniformly fatal, and that surviving infants may be apparently normal or may have varying degrees of neurologic sequelae. The present report of three patients with cytomegalic inclusion disease further emphasizes the variations in severity of the sequelae which may occur in those infants who survive beyond the neonatal period.

CASE REPORTS

CASE 1.*—A. L., a white male infant, was born on Jan. 1, 1953, two weeks after the calculated date of delivery. The pregnancy had been uneventful. An older sibling, 2 years of age, was living and well.

The weight at birth was 4 pounds 15 ounces. The infant was covered with petechiae and purpuric spots at the time of delivery. At 2 hours of age he received a transfusion of 50 c.c. of whole blood, type O, Rh negative.

Physical examination less than twenty-four hours after delivery revealed innumerable petechiae over the body, many of which appeared to be relatively old. His general condition was quite good and there was no apparent icterus. The spleen extended almost to the left iliac crest and the edge of the liver was 1.5 cm. below the right costal margin. His hemoglobin was 17.1 grams per cubic millimeter; throughout the remainder of this hospitalization it varied from 10 to 15 grams per cubic millimeter. The red blood cells were 4,650,000 per cubic millimeter, and white blood cells 13,150 per cubic millimeter, with 41 per cent neutrophils, 54 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils. There were 12 nucleated red blood cells per 100 white blood cells.

On the third day of life the petechiae had decreased somewhat in number but the spleen had increased in size. There was no icterus. Smear of the peripheral blood revealed 20 per cent neutrophils and 80 per cent lymphocytes and monocytes. Repeated aspirates of the right tibia failed to yield bone marrow. Urinalysis revealed 2 plus albumin, no sugar, 1 to 2 white blood cells and 0 to 2 red blood cells per high-power field. Smears of the urinary sediment revealed only a small number of poorly preserved epithelial cells. The following day smears of the urinary sediment stained with hematoxylin and eosin revealed multiple epithelial cells containing large purple intranuclear inclusion bodies which almost filled the nucleus; a few cells contained multiple small purple granules suggestive of intracytoplasmic inclusion bodies. Roentgen films of the chest revealed a fine mottling throughout the lung fields, suggestive of patchy atelectasis. White blood cells during the next ten days varied from 8,250 to 16,400 per cubic millimeter, with a predominance of lymphocytes, many of which appeared to be atypical forms. Thrombocytopenia persisted, the platelets varying from 30,550 to 63,800 per cubic millimeter. Smears of the urinary sediment on six different days, stained with hematoxylin and eosin or by Papanicolaou's technique, failed to reveal inclusion bodies. In every instance, however, either there were no epithelial cells present or the few which were visualized were poorly preserved. The temperature fluctuated between 96.8° and 103.6° F. but was usually between 98° and 100° F. Weight fell to 4 pounds 5 ounces on the second day of life; subsequently it rose steadily to 5 pounds 13 ounces on January 16, at which time he was discharged from the hosptial.

*We are indebted to Dr. Robert Shelly and Dr. Nathan J. Smith for the data concerning this infant.

He was readmitted two weeks after discharge from the nursery. During the interim he had been fussy and there had been intermittent periods of fever, but his formula had been taken well. Physical examination at the time of admission revealed a weight of 7 pounds 1½ ounces, temperature 100° F., pulse 130, and respirations 36 per minute. He cried lustily when examined. A generalized petechial rash was present. The edge of the liver was three fingerbreadths below the right costal margin and the spleen extended below the level of the iliac crest. There were bilateral hydroceles and bilateral inguinal hernias. Coarse rhonchi were audible in the upper aspects of the lungs. The circumference of the head was 12½ inches and that of the chest was 13½ inches. The pupils were equal and reacted to light; the ocular fundi revealed no abnormalities. The neurologic examination was interpreted as normal.

The hemoglobin was 7.2 grams per 100 c.c.; red blood cells, 2,250,000 per cubic millimeter; white blood cells, 11,350 per cubic millimeter, with 15 per cent neutrophils, 84 per cent lymphocytes, and 1 per cent monocytes. Most of the lymphocytes appeared atypical. There were 7 normoblasts per 100 white blood cells and the reticulocytes were 4 per cent. Platelets numbered 21,000 per cubic millimeter of blood. Routine urinalysis revealed no abnormalities except for the presence of 1 plus albumin. Culture of the blood yielded no growth.

Roentgen films of the chest on February 2 revealed an abnormal density at the medial aspect of the right base, probably representing a small area of pneumonia. Subsequent films revealed densities at the base of the left lung and in the right upper lobe, with clearing of the lesion in the right base. The skeletal survey was interpreted as normal, but roentgen films of the skull revealed rather severe microcephaly with patent cranial sutures and anterior and posterior fontanels. No intracranial calcifications were visualized.

Throughout this period of hospitalization the temperature ranged between 97.4° and 104° F. The respirations rose to 104 per minute and were associated with severe costal retractions. His cry was high pitched and the reflexes were hyperactive. Focal spastic convulsions of the right upper extremity were noted. New petechiae appeared on several occasions.

An electroencephalogram was interpreted as normal for his age. The hemoglobin and white blood count did not vary significantly from those at the time of admission. Repeated routine urinalyses were normal except for the presence of 1 plus albumin. Bone marrow aspirated on February 11 revealed no abnormalities. He received Aureomycin, penicillin, and two transfusions during his hospitalization and was transferred to St. Christopher's Hospital for Children at the age of 6 weeks.

Physical examination at the time of admission was essentially unchanged from that previously recorded, except for the presence of a soft, grade 2 systolic murmur along the left sternal border. The temperature was 99° F., pulse 140 per minute, respirations 52 per minute. Length was 19¾ inches and weight, 8 pounds 4 ounces. The Moro reflex was very poor. The eyes did not react to or follow light and there was no social smile. The ocular fundi revealed no abnormalities. There was a suggestion of hyperactive reflexes.

Laboratory studies were essentially unchanged from those obtained at the previous hospital. The platelets, however, had risen to 140,000 per cubic millimeter. Spinal fluid on February 17 was normal except for the presence of 190 mg. of protein per 100 c.c. Culture of the spinal fluid yielded no growth. The serum protein was 6.34 grams per cent, calcium 11.1 mg. per 100 c.c., and phosphorus 6.65 mg. per 100 c.c. Complement fixation test of the serum was negative for toxoplasmosis. Roentgen films of the chest on February 16 revealed a homogeneous density in the right upper lobe. Films

of the skull and long bones revealed no abnormalities. Electroencephalogram nine days later revealed random 3 to 7 per second waves over the left cerebral hemisphere and virtual absence of electrical activity over the right cerebral hemisphere. Auditory stimuli failed to alter this pattern, which was repeated on two different days. His general condition improved following the administration of Neo-Penil and he was discharged on Feb. 25, 1953.

He was readmitted on three subsequent occasions. On the first of these (March, 1953) an infarcted right testis associated with an incarcerated inguinal hernia was resected. Subdural taps yielded a free flow of crystal-clear fluid containing 63 mg. of protein per 100 c.c. from the right side. No fluid was obtained on the left.

In May the circumference of the head was 15½ inches; those of the chest and abdomen were each 17½ inches. He did not respond to sound, light, or touch. Hepatomegaly and splenomegaly were still present. The anterior fontanel was bulging and tense, and there was moderate nuchal rigidity. There was generalized tremor and the upper extremities were rigid. Lumbar puncture yielded a small amount of clear fluid under low pressure. The fluid contained 19 lymphocytes per cubic millimeter and protein of 60 mg. per 100 c.c. Because the convulsions and tense fontanel persisted following the lumbar puncture, "subdural" taps were performed with the removal of 50 c.c. of clear fluid from the right "subdural" space; no fluid was obtained on the left. The fluid contained 50 mg. of protein per 100 c.c. and 29 mg. of sugar. Following this procedure the anterior fontanel was depressed. Smears of the fluid stained with hematoxylin and eosin revealed a number of cells with large, deep purple intranuclear inclusions separated by a clear halo from the nuclear membrane (Fig. 1).

Smears of the urinary sediment on two occasions revealed almost no recognizable epithelial cells. Repeated episodes of cyanosis, tremors, and bulging of the anterior fontanel were relieved by "subdural" taps, as much as 100 c.c. of yellow fluid being removed on one occasion. The fluid became xanthochromic and its content of protein rose to 160 mg. per 100 c.c. Roentgen films of the skull revealed an abnormal increase in the size of the head since the last examination, with separation of the coronal and sagittal sutures. Films taken after the injection of air into the right subdural space revealed a large accumulation of air with a fluid level. The platelets now numbered 404,000 per cubic millimeter; other laboratory findings were essentially unchanged. Attempts to isolate a virus in tissue cultures of HeLa cells inoculated with "subdural" fluid and with urine which has been stored in the freezer were unsuccessful.

Fig. 1.—Cell from fluid obtained by "subdural" tap. The nuclear membrane, which in some areas is indistinct, is everywhere separated from the large intranuclear inclusion. (×910; reduced ⅓.)

He was last admitted in July, 1953. Physical examination revealed an irritable, spastic infant weighing 17 pounds 8 ounces. The skin was covered with fine petechiae. (No petechiae had been observed during his past three periods of hospitalization.) The circumference of his head was now 19 inches, the anterior fontanel was large and tense and the cranial sutures were separated. Funduscopic examination revealed a round, well-circumscribed

patch of lighter color in the right choroid. The edge of the liver was 3 cm. below the right costal margin. The spleen was not palpable. The extremities were spastic, with hyperactive deep tendon reflexes. Platelets were 88,000 per cubic millimeter. Roentgen films of the skull revealed no evidence of intracranial calcification. He died in a nursing home Dec. 27, 1953.

Post-mortem examination revealed a fairly well-developed infant measuring 29 inches in length. The circumference of the head was 20¾ inches, and that of the chest was 18½ inches. The anterior fontanel was widely patent. The spleen weighed 50 grams, as compared with a normal weight of 26 grams. The liver weighed 415 grams, as compared with a normal weight of 288 grams. The combined weight of the kidneys was 59 grams, as compared with a normal weight of 71 grams; grossly they revealed no abnormalities. The sagittal and lambdoidal sutures were slightly separated. An encapsulated subdural hematoma, 5 by 3 by 1 cm., was present at the inferior aspect of the left coronal suture but no subdural hemorrhage or fluid was present on the right side. The falx cerebri was intact. There was no septum pellucidum, the two lateral ventricles forming a huge, common chamber filled with clear, colorless fluid. Superiorly nothing suggesting a cerebral hemisphere was present on the right, the ventricular cavity being covered by a thin, delicate, transparent membrane. On the left this membrane was slightly thicker and here its inner surface suggested an ependymal lining. The basal ganglia on either side were clearly visualized at the base of the common ventricular chamber. Punctate yellow deposits of calcium were present on the ependymal surfaces of the basal ganglia and in the membrane covering the superior surface of the right half of the common ventricular chamber. The cerebellum was normal or possibly somewhat small. The foramina of Luschka and Magendie were patent. Recognizable cerebral substance on the right was confined to the base of the occipital lobe, where a small amount of cerebral substance without distinct convolutions was present; this measured less than 0.1 cm. in thickness. At the base of the left cerebral hemisphere multiple small, poorly developed gyri were present from the frontal to the occipital lobes, the entire thickness not exceeding 0.7 cm. and in some areas being much thinner. A slitlike cavity 0.8 cm. long, apparently representing the remnant of the third ventricle, was present in the midline between the basal ganglia. Section through the region of the mesencephalon failed to reveal an aqueduct of Sylvius.

Histologic examination revealed focal infiltrates of lymphocytes in the walls of the bronchioles and adjoining the interlobular septa; there was no apparent thickening of the interalveolar septa. A mild infiltrate of lymphocytes was present in the interstitial tissue of the myocardium in some areas. The splenic trabeculae were prominent and approximated, and there were severe lymphoid hyperplasia and hemorrhage throughout the red pulp. There was no portal fibrosis or any significant inflammatory infiltrate in the portal triads. Multiple lymphoid nodules, some with germinal centers, were present in the renal cortex (Fig. 2); inclusion bodies were not identified in the immediate vicinity of these nodules. Occasional epithelial crescents were present, as well as a number of partially or completely hyalinized glomeruli. Multiple lymphoid nodules were present in the submaxillary glands. Only very rarely were inclusion bodies identified in the viscera, these being limited to Brunner's glands, kidneys (Fig. 3), submaxillary gland, and thyroid. Except in the submaxillary gland, there was no significant infiltrate of lymphocytes about the inclusion-bearing cells.

Sections of the "cerebral cortex" on the left revealed multiple perivascular foci of lymphocytes with occasional

Fig. 2.

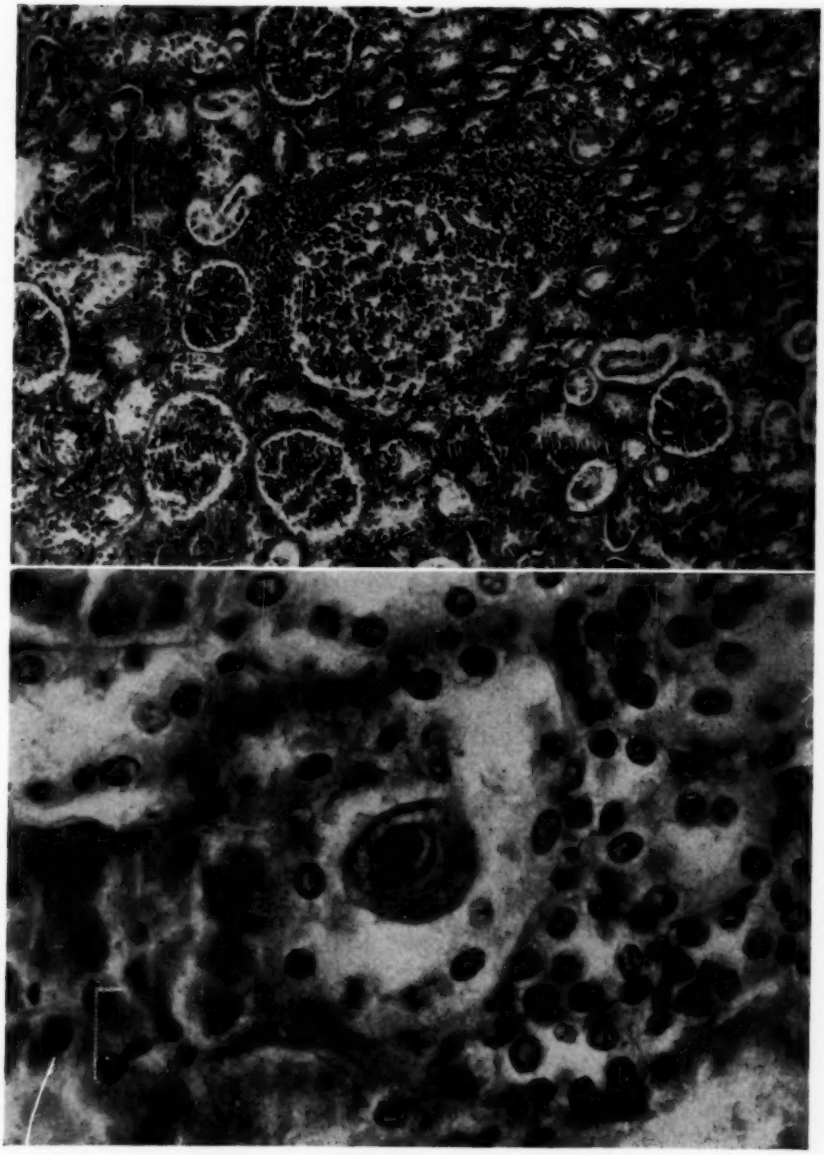

Fig. 3.

Fig. 2.—Lymphoid aggregate in the renal cortex. (×164; reduced ¼.)
Fig. 3.—Desquamated renal tubular epithelial cell containing an intranuclear inclusion body. (×910; reduced ¼.)

small foci of calcification located especially in the subependymal zone. There was a mild infiltrate of lymphocytes in the pia. Beneath this were increased vascularity and glial proliferation in the cortex.

Sections of the basal ganglia and mesencephalon revealed a distorted aqueduct of Sylvius which was subdivided into multiple chambers by proliferation of glial fibers, isolating cords, nests, and small channels of ependymal cells. Focal and perivascular infiltrates of lymphocytes were present in the mesencephalon. There were extensive necrosis, calcification, and subependymal glial proliferation with isolation of nests of ependymal cells in the region of the thalamus. No inclusion bodies were identified in the central nervous system.

The final diagnoses were (1) cytomegalic inclusion disease with residual inclusion bodies in the salivary glands, kidneys, pylorus, and thyroid; (2) multiple lymphoid nodules with germinal centers involving several viscera; and (3) stenosis of the aqueduct of Sylvius with hydranencephaly and extensive necrosis and calcification in the region of the basal ganglia and in the small amount of residual cerebral tissue at the base of the "cerebral hemispheres."

CASE 2.—W. M., a white male infant, was born on Nov. 4, 1954, after an uneventful pregnancy of thirty-seven weeks' duration. The mother was 18 years of age, para 0, gravida i, and had noted no unusual illnesses during pregnancy. Delivery was spontaneous; the infant's weight at birth was 5 pounds 13 ounces. He cried spontaneously immediately following delivery but cyanosis and scattered petechiae on his forehead were noted shortly after delivery. Icterus was first noted at about 12 hours of age; at this time additional petechiae appeared on the trunk and extremities. No other evidences of a bleeding tendency were noted and no further petechiae appeared. Cyanosis, which initially was controlled by the administration of oxygen, subsequently disappeared. The infant had no evidence of anemia and the direct antiglobulin reaction (Coombs) was negative. Since he was eating well and appeared to be in good health except for persistent icterus he was discharged from the hospital on the fifth day of life.

He did well while at home and the mother believed that the stools and urine were of normal color. Icterus persisted, however, and because of this he was referred to St. Christopher's Hospital for Children at the age of 7 weeks. Physical examination revealed a moderately icteric white male infant who did not appear acutely ill. His weight was 7 pounds 11 ounces, temperature 100.2° F., pulse 122, and respirations 32 per minute. The edge of the liver was 2 cm. below the right costal margin and the tip of the spleen 4 cm. below the left costal margin. The remainder of the physical examination revealed no abnormalities.

Fig. 4.—Intranuclear inclusion body in a cell in the urinary sediment. (×1,125; reduced ⅛.)

On the third day of hospitalization his temperature rose to 102° F. Culture of the blood at this time yielded pneumococci. He responded favorably to the administration of tetracycline, becoming afebrile two days after the onset of therapy. Smears of the urinary sediment obtained on the second day of hospitalization revealed the characteristic cells of cytomegalic inclusion disease (Fig. 4).

The hemoglobin was 8.9 grams per 100 c.c. There were 18,800 white blood cells per cubic millimeter with 47 per cent segmented neutrophils, 4 per cent

band forms, and 49 per cent lymphocytes. Platelets were 284,000 per cubic millimeter, and reticuloeytes were 10.6 per cent. The total serum bilirubin was 5.4 mg. per 100 ml., of which 4.7 mg. were direct and 0.7 mg. indirect. Thymol turbidity was 7.75 units, and cephalin flocculation was 3 plus. Serologic tests for syphilis were nonreactive. Repeated urinalyses were negative, although inclusion bodies were demonstrated in the urine on three different days. Attempts to isolate a virus in tissue cultures of HeLa cells inoculated with urine which had been stored in the freezer were unsuccessful. The direct antiglobulin reaction (Coombs) was negative. No agglutinins for platelets were demonstrable. Examination of the cerebrospinal fluid revealed no abnormalities; no inclusion bodies could be demonstrated in smears of this fluid. The osmotic and mechanical fragility of the patient's erythrocytes was increased.

Following completion of the above studies the patient was discharged and has been seen by one of us (A. E. M.) at periodic intervals. Subsequent laboratory studies are recorded in Table I.

His somatic development, with the exception of the head, has been within normal limits. His length at 11 months of age was 27 inches, weight 16 pounds 4 ounces, and the head circumference 17 inches. At 19 months his head measured 17¾ inches in circumference; this is below the third percentile for this age. Hepatomegaly and splenomegaly have persisted, each organ being about 3 cm. below the costal margin at 19 months of age. His mental and motor development has been retarded but with considerable scatter. Thus, at 4 months of age he did not hold up his head while in the prone position, but by the age of 5 months he held up his head and was able to roll over. He did not smile until 5 months of age. At the age of 8 months he did not sit alone and had poor control of his head when propped in the sitting position. At this age, however, he reached well for objects. At 11 months of age he sat alone but did not stand, even with support. At 19 months he walked well with support, spoke four words, including "Mommy" and "Daddy," and had a good pincer grasp. He still appeared to have disturbed equilibrium and fell easily.

He was seen at 26 months of age, at which time an inguinal hernia was repaired. Histologic examination of skin, skeletal muscle, and the hernial sac revealed no evidence of inclusion bodies. At this time he had an apparently normal vocabulary, used simple sentences, built a tower of five blocks and passed the form board portion of the developmental examination according to the technique of Gesell. His head measured 18¼ inches in circumference and his height was 34¼ inches. Hepatomegaly and splenomegaly were somewhat less severe than at 19 months

TABLE I. LABORATORY DATA CONCERNING W. M. (CASE 2)

DATE	AGE	HEMOGLOBIN GM./100 ML.	TOTAL BILIRUBIN MG./100 ML.	CEPHALIN FLOCCULATION	THYMOL TURBIDITY UNITS	URINARY INCLUSIONS
12/28/54	8 wk.	8.9	5.4	3+	7.75	Numerous
1/ 6/55	9 wk.	9.2	2.8	4+	12.0	Easily found
3/ 3/55	4 mo.	9.6	0.6	4+	7.75	Easily found
4/16/55	6½ mo.	10.4	0.4	3+	2.8	Present but poorly preserved
7/ 5/55	9 mo.	10.2	--	Neg.	3.4	No studies
9/ 8/55	11 mo.	10.8	0.4	--	--	Rare, poorly preserved
6/21/56	19 mo.	11.2	0.4	2+	4.0	No studies
1/20/57	26 mo.	10.2	0.6	Neg.	2.0	None seen

of age. The only neurologic abnormality was a wide-based, slightly ataxic gait. In other respects he appeared normal, although psychologic evaluation was unsatisfactory at this time.

CASE 3.—R. F., a white male infant, was born at term on March 7, 1954, after an uneventful pregnancy. The mother was 21 years of age, para 0, gravida i. Delivery was spontaneous. The infant's weight at the time of birth was 6 pounds. Although he cried spontaneously and was not cyanotic, petechiae and purpuric spots were noted over the entire body immediately after birth. The tip of the spleen was 2 cm. below the left costal margin; the liver was not palpable. Icterus was noted at 12 hours of age. His hemoglobin was 15.8 grams per 100 c.c., and platelets 38,000 per cubic millimeter. The direct antiglobulin reaction (Coombs) was negative. On the third day of life examination of the urinary sediment by Dr. Lester Rauer at Northwestern Hospital revealed the presence of numerous large cells with prominent large intranuclear inclusion bodies (Fig. 5).

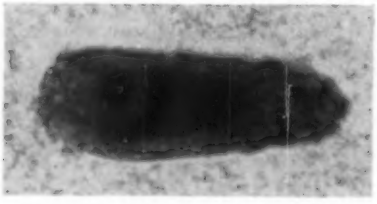

Fig. 5.—Cell in the urinary sediment containing an intranuclear and multiple cytoplasmic inclusion bodies (×1,120; reduced ⅛.)

The infant failed to gain normally, although he took his feedings well and did not appear acutely ill. Icterus persisted for three weeks; the highest recorded level of the serum bilirubin was 9 milligrams per cent. Thrombocytopenia persisted for three weeks; subsequently the platelets have been normal. Except for the petechial and purpuric rash no evidences of bleeding were noted. Roentgenograms revealed no intracranial calcification or any abnormalities of the long bones. For the first month of life his weight did not exceed 6 pounds 8 ounces. Following this he began to gain steadily, so that at the time of discharge, at the age of 46 days, his weight was 8 pounds 2 ounces.

Between the time of discharge from the hospital and the time at which he was seen at St. Christopher's Hospital for Children he was examined at periodic intervals by Dr. Elmwood Force, who noted an average gain in weight and no recurrence of icterus or purpura. The infant did not sit alone until 9 months of age, but walked and was toilet trained at the age of 15 months. The development of speech was slow, so that at the age of 20 months his vocabulary was limited to three words.

Through the courtesy of Dr. Force he was examined at St. Christopher's Hospital for Children at the age of 20 months. At this time he was an alert-appearing infant weighing 26 pounds and measuring 33¼ inches in length. The circumference of his head was 18½ inches. The edge of the liver, which was smooth and soft, was 2 cm. below the right costal margin, and the tip of the spleen was 3 cm. below the left costal margin. The remainder of the physical examination, including examination of the ocular fundi and neurologic examination, revealed no abnormalities. The serum bilirubin was 0.6 mg. per 100 ml. and the cephalin flocculation and thymol turbidity tests were normal. His hemoglobin was 13.1 grams per 100 c.c.; there were 10,400 white blood cells per cubic millimeter, with 57 per cent lymphocytes, 41 per cent neutrophils, and 2 per cent eosinophils. Reticulocytes comprised 0.4 per cent of the erythrocytes, and the platelets were 284,000 per cubic millimeter. Roentgenographic studies of the skull, long bones, and chest revealed no abnormalities.

Developmental analysis at the age of 20 months utilizing the method of Gesell was performed by Dr. Milton Sarshik and revealed a motor level of 21 months, an adaptive level of 21 to

24 months, a language level of 15 months and a personal-social level of 24 months. The unusual factors noted were retardation in some motor activities and retardation in language, with normal or superior adaptive ability, producing a "scatter" suggestive of organic disease of the central nervous system.

The patient, who is now 35 months of age, was seen briefly in his home at the age of 27 months. At this time he spoke sentences of two to three words and climbed stairs one step at a time. His parents felt that his vocabulary was limited in comparison to neighboring children of comparable age.

DISCUSSION

Survival of infants in whom the diagnosis of cytomegalic inclusion disease has been made by demonstration of inclusion bodies in the urinary sediment has been reported only rarely.[8, 9, 10] In the few infants who have survived, varying degrees of neurologic abnormality have usually been noted, although Birdsong and co-workers[10] have described an infant who was apparently well at the age of 10 months. In the infant described by Gallager[7] the diagnosis was established by histologic examination of excised pulmonary tissue, and there is no record of the presence or absence of inclusion bodies in the urine. The three patients here reported demonstrate the extremes of neurologic involvement which may occur, varying from hydranencephaly with extensive cerebral destruction to fairly minimal retardation. The two infants who are still living have ultimately attained heights and weights within the normal range for their age.

Several other aspects of the disease as noted in these infants appear to be worthy of comment. Thrombocytopenia persisted until the third to the fifth month in the most severely involved infant and recurred at 7 months of age. The platelets returned to normal levels at 7 weeks of age in one infant, while in the other the duration of thrombocytopenia is not known. Petechiae were noted in all three infants at or shortly after delivery, but in one they were few in number. Icterus was noted within the first twelve hours of life in two of the three infants. It persisted for about three weeks in one infant and disappeared between 9 weeks and 4 months of age in the other. In the latter infant the cephalin flocculation test was 2 plus at 15 months of age but was negative at 26 months of age. In the most severely involved infant there is no record of the occurrence of icterus at any time.

Anemia was noted in all of the infants. In one there was evidence of a hemolytic process at 7 weeks of age; the hemoglobin was 8.6 grams per 100 c.c. and the reticulocytes, 10 per cent. The osmotic and mechanical fragility of the red blood cells of this infant was increased at 7 and 8 weeks of age, but had returned to normal at 4 months. The mechanism of this increased fragility is not known. No hemagglutinins were demonstrable in saline or in glue or by the direct antiglobulin technique (Coombs).

Inclusion bodies were still demonstrable in the urine of one infant at 11 months of age. In the most severely involved infant the later specimens of urine which were examined were unsatisfactory, the epithelial cells being either too poorly preserved or too few in number to permit identification of inclusion bodies. It should be emphasized that only fresh specimens of

urine are satisfactory for examination, since the cells deteriorate when the urine is allowed to stand for some time. Inclusion bodies were demonstrated in fluid (possibly ventricular) obtained by "subdural" tap from one infant at 5 months of age, and a few inclusion bodies were demonstrable in renal tubular epithelial cells at the time of autopsy at 1 year of age. Thus, as earlier demonstrated by Margileth,[8] it seems possible that the diagnosis may still be established in infants beyond the newborn period.

SUMMARY

Three patients in whom the diagnosis of cytomegalic inclusion disease was established during life are reported. The most severely involved infant died at 1 year of age. Post-mortem examination revealed hydranencephaly with cerebral calcifications and the presence of small numbers of inclusion bodies in scattered viscera. Focal infiltrates of lymphocytes in a number of viscera were noted and may represent reaction to pre-existing inclusion-bearing cells.

The two surviving infants are 26 and 35 months of age at this time. Their mental and motor development has been retarded but has revealed considerable scatter, and the degree of retardation is certainly not striking.

Inclusion-bearing cells were still demonstrable in the urine of one infant at 11 months of age. Similar cells were present in very small numbers in renal tubular epithelial cells at the time of necropsy in the infant who died at 1 year of age. The diagnosis may be established by examination of smears of the urinary sediment several months after birth.

The disease is not always associated with severe mental and motor retardation.

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A COMPARISON OF INTRAMUSCULAR AND ORAL BENZATHINE PENICILLIN G IN THE TREATMENT OF STREPTOCOCCAL INFECTIONS IN CHILDREN

B. B. Breese, M.D., and Frank A. Disney, M.D.
Rochester, N. Y.

THIS study was planned to determine whether the oral or the parenteral use of penicillin is superior in the treatment of beta hemolytic streptococcal infections in children. We also hoped to find the best practical dosage schedule for oral penicillin. Because previous experience had convinced us that a single intramuscular dose of 600,000 units of benzathine penicillin G was a highly effective and practical method of therapy in these infections,[1] we compared it with the same penicillin salt in oral form.

MATERIAL AND METHODS

The children in this study were among the private pediatric patients of the writers, observed from Nov. 1, 1954, through June, 1955. When a beta hemolytic streptococcal infection in one of these children was suspected, a throat culture was taken. If, at the time, our clinical opinion was that the infection was probably due to this organism, treatment was started. Otherwise, we awaited the result of the culture the next day before starting specific therapy. The home and office methods of culture and isolation of strains have been described previously.[1] Only children with positive cultures were included in the study. Whether a patient was to receive oral or parenteral penicillin was determined at the time of treatment by drawing at random a previously labeled card. For the first five months of the study, equal numbers of "parenteral" and "oral" cards were used, but in the last three months about twice as many "oral" cards as "parenteral" cards; but they continued to be selected by chance throughout the study. The oral dosage of penicillin was increased three times as results indicated each time that the previous dosage had been inadequate. There were 463 patients in the series. Of these, 182 were treated by a single dose of benzathine penicillin G (Bicillin injection) intramuscularly and the remaining 281 were given various oral doses of benzathine penicillin G. Throughout the study, with a few exceptions, all children under 4 years of age who were given oral penicillin received a very pleasant-tasting liquid suspension of oral benzathine penicillin G containing 300,000 units per teaspoon (Bicillin suspension "300").

From the Department of Pediatrics, University of Rochester School of Medicine and Dentistry.

This study was supported by a grant from Wyeth Laboratories, who also supplied the benzathine penicillin G (Bicillin) used in this study.

The grouping and typing of streptococci were done by The Streptococcal Typing Laboratory, United States Public Health Service, Chamblee, Ga., under the direction of Dr. Elaine Updyke and by Dr. Harry Feldman, State University of New York School of Medicine, Syracuse, N. Y.

The media were supplied by the Rochester Health Bureau.

All others received tablets of benzathine penicillin G containing 200,000 units each (Bicillin tablets). The various doses utilized are indicated in Table I. The tablets and suspension were given at 8 A.M., 2 P.M., and 8 P.M. When four tablets were given daily, the same times were utilized except that two tablets were given at 8 P.M.

Patients were observed for a period of two months following medication. They were checked in the office three weeks after therapy. At this time, each child was examined by one of us, a culture of the throat taken, the urine examined, and a microsedimentation rate done by the method of Landau.[2] They were also questioned in regard to symptoms suggestive of illness, such as reactions to medication, nephritis, or rheumatic fever. Six weeks after the beginning of medication, our bacteriologist visited the home and took a culture from the patient's throat as well as from the sibling's. She also again inquired about taking the medication, reactions to it, and other illness. In addition, we were notified if the children became ill again; consequently, very few streptococcal infections escaped our observation.

All patients at the end of a two-month period were classified as either "cured," "recurrent," or "carrier." "Cured" patients were those who were well, or who may have had some unrelated disease (for example, measles), and whose follow-up cultures were negative. "Recurrent" patients were those who, after therapy, developed a disease with signs and symptoms that were consistent with a streptococcal infection, and from whom a hemolytic streptococcus was isolated. A "carrier" was one who, though apparently not ill, was found to have a positive throat culture at some time during the period of observation after treatment. Both of these last groups were considered to be therapeutic failures. If an antibiotic was again administered for any type of infection during the two months of follow-up, the period of observation was considered terminated at that time. However, no patient was included in the series unless he had been observed for at least eleven days. Of this series 91 per cent were followed for longer than three weeks, and 74 per cent for more than five weeks.

Table I. Dosages, Schedule, and Time Given for Various Penicillin Preparations

PERIOD USED	FORM AND AMOUNT BENZATHINE PENICILLIN G	DAYS GIVEN	TOTAL DOSE IN UNITS	NUMBER PATIENTS
Nov. to June	1 c.c. I.M., 600,000 U.	1	600,000	182
Nov. to June	60 c.c. suspension, 300,000/5 c.c.	8	3,600,000	43
Nov. to March	24 tablets, 200,000 U.	8	4,800,000	90
March to June	30 tablets, 200,000 U.	10	6,000,000	105
May to June	40 tablets, 200,000 U.	10	8,000,000	43
			Total	463

Data were coded and punched on International Business Machine cards and were analyzed for them.

RESULTS

Age.—The greatest number of patients was seen in the 5- and 6-year-old age groups. There were eighty-eight patients in each of these age brackets; next most common were the 7-year-olds, with sixty-six. Together these three age groups represent about 50

per cent of the entire series. There were seventy-seven (17 per cent) under the age of 4, and forty-four (10 per cent) 10 years of age or older.

Sex.—The sex distribution was equal.

Diagnosis.—Approximately 90 per cent of the primary diagnoses in each treatment group were either tonsillitis, pharyngitis, or scarlet fever.

Culture.—In the vast majority of patients (85 per cent), the cultures for hemolytic streptococci were strongly positive (3 or 4 plus). Almost all (93 per cent) strains isolated were grouped and typed. Of those that were grouped, 95 per cent were Group A. Of the Group A, approximately half (48 per cent) were not typable. There was no essential difference in the distribution of various groups or types of streptococci in the three different therapeutic series.

Clinical and Bacteriologic Results of Treatment.—With all schedules used, the immediate effect on the clinical disease was dramatic—the child rapidly (within forty-eight hours in most instances) appeared to recover completely. However, final results of the various schedules of therapy are compared by two-month periods in Table II. These figures suggest, judging by the cure rate obtained during the *same period of time,* that the injection form of therapy is superior to the oral form. Compared with the liquid medication given to those children under 4, the difference is only 6.9 per cent and is not statistically significant ($p = 20$). Compared with the 24 tablets given in eight days (4,800,000 units) and with 30 tablets (6,000,000 units) given in ten days, the difference is about 18 per cent in each case and is highly significant ($p = .02$ and .03, respectively). With 40 tablets (8,000,000 units) given in ten days, the difference of 11 per cent in favor of the Bicillin injection is suggestive but not statistically significant ($p = 7$). For the group as a whole, 73.2 per cent were classified as "cured," 18.1 per cent were "recurrences," and 8.7 per cent were "carriers."

These "cure rates" do not take into account the fact that an appreciable number of recurrences or carriers were found to have streptococci of a different type than the originally infecting strain and were thus clearly new infections and not therapeutic failures. In sixty-five of the 125 bacteriologic relapses, it was possible to determine whether or not they were caused by the original type. In twenty-eight cases (43 per cent of the sixty-five) they were found to be due to a type different from the original infecting organism. For this reason, the true "cure rate" is higher than indicated in Table II, since approximately 40 per cent of those cases classified as "failures" were actually due to unrelated new infections. This fact did not seem to affect materially the relative merits of the various therapeutic schedules used.

Reactions.—In those receiving the benzathine penicillin G intramuscularly, local reactions at the site of injection were common for a few days afterward. These varied from slight soreness to discomfort intense enough to make walking difficult. None was serious. In those receiving the penicillin orally, mild diarrhea was seen fairly commonly, but in no case was it severe.

Allergic reactions to penicillin were uncommon. Although all patients

TABLE II. THE PERCENTAGE OF "CURED" CHILDREN TREATED BY INTRAMUSCULAR AND ORAL BENZATHINE PENICILLIN G

PERIOD	600,000 U., I.M., ONCE			3,600,000 U., P.O., 8 DA.			4,800,000 U., P.O., 8 DA.			6,000,000 U., P.O., 10 DA.			8,000,000 U., P.O., 10 DA.		
	TOTAL NO.	NO. CURED	PER CENT CURED	TOTAL NO.	NO. CURED	PER CENT CURED	TOTAL NO.	NO. CURED	PER CENT CURED	TOTAL NO.	NO. CURED	PER CENT CURED	TOTAL NO.	NO. CURED	PER CENT CURED
Nov.-Dec.	28	23	82	4	3	75	19	9	47	–	–	–	–	–	–
Jan.-Feb.	64	50	78	13	7	54	57	37	65	–	–	–	–	–	–
March-April	60	47	78	21	17	81	14	9	64	68	42	62	–	–	–
May-June	30	28	93	5	5	100	–	–	–	37	27	73	43	35	82
Total	182	148	81.3	43	32	74.4	90	55	61.1	105	69	65.7	43	35	81.4

known to be allergic to penicillin were excluded from the study and treated in some other manner, no attempt was made to exclude those known to have such allergies as those manifested by a history of hay fever, asthma, eczema, or hives. That the series contained an appreciable number of such patients was indicated by the fact that in a random sample of 100 patients in the series carefully questioned about hay fever and asthma eight suffered from these diseases.

Among the 463 attacks treated, adequate histories in regard to the post-therapy occurrence of hives or serum sickness-like reactions were obtained in 448. This revealed that four children definitely developed urticarial-like reactions following the penicillin. Another had a very questionable reaction, and one had hives one month later thought to be due to some cause other than penicillin. There were no serum sickness-like reactions. In all six children the reactions followed oral penicillin—none occurring in those receiving benzathine penicillin by injection. Thus, the allergic reaction rate in the entire series was approximately 0.9 per cent.

COMMENT

Numerous studies have indicated that both oral penicillin and intramuscular benzathine penicillin G are effective against beta hemolytic streptococcal infections. However, comparative studies of the relative effectiveness of the two methods of therapy are rare. Mohler and co-workers[3, 4] observed the failure of patients to take oral penicillin and compared the therapeutic value of 200,000 units of potassium penicillin G three times daily for seven days with that of 600,000 units of benzathine penicillin G by intramuscular injection. Their subjects were children from a low-income population in Boston observed at the same time that our study was being carried out among private pediatric patients in Rochester, New York. They found that approximately one-third of their patients did not take the prescribed amount of medication orally for various reasons. Among them, one of the major problems was the cost of the oral medication. The investigators used somewhat different and less stringent criteria for the effectiveness of therapy but based the results largely on the bacteriologic relapse rate, much as we did. In their series the "cure rate" was 82.7 per cent among those taking the medication orally and 94.4 per cent of those receiving benzathine penicillin G by injection.

In our cases, questioning indicated that it was relatively rare for patients not to take the oral medication as prescribed. Nonetheless, considering the different populations and methods of study, our results are in remarkable agreement with theirs regarding dosage schedules.

However, our observations indicate that with an increase in dosage and duration of therapy the two forms of therapy can be brought into closer approximation in effectiveness, although there was suggestive evidence, in this series, to indicate a slight advantage in favor of the intramuscular route over the oral route.

Markowitz and associates[5] studied the relative merits of benzathine penicillin G orally and parenterally in preventing streptococcal infections and rheumatic fever recurrences in a group of 106 children who had had rheumatic fever. They gave 200,000 units

orally once daily or 1,200,000 units intramuscularly once a month. When the children took the oral medication regularly, there was no essential difference in the incidence of streptococcal infections in the two groups or in the recurrence rate of rheumatic fever. One patient of the fifty taking oral penicillin and four of the fifty-six receiving parenteral penicillin had allergic reactions. Local reactions were frequent in the latter group. In contrast to our study, however, the dosage of oral penicillin was smaller and the parenteral dosage larger.

Rammelkamp and his group of associates[6] at the Fort Warren Air Base reported on a prophylactic program of oral penicillin and benzathine penicillin G. The oral dosage used was 250,000 units of buffered potassium crystalline penicillin G twice daily, whereas benzathine penicillin G was given intramuscularly in a single dose of 600,000 or 1,200,000 units. They concluded that the oral preparation was not quite so effective prophylactically as the intramuscular doses. In eliminating streptococci from the throat of carriers, the dosage of 1,200,000 units of benzathine penicillin G was best, whereas the oral dose for ten days and the intramuscular dose of 600,000 units were about equally effective. In seventy-one carriers treated with the larger intramuscular dose there were no recurrences of the same type at the follow-up examination, whereas there were three among sixty-nine receiving the smaller intramuscular dose observed at the same time (twenty-one days after treatment), and two among seventy-one treated with the oral medication and examined twenty-eight days later. The chief toxic symptoms noted in the young adults studied were urticaria or angioneurotic edema. These occurred in 4.06 per cent of those receiving 1,200,000 units and in 1.47 per cent of those receiving 600,000 units of benzathine penicillin G intramuscularly, and in 0.83 per cent of those receiving oral penicillin.

In another prophylactic study of air force trainees heavily exposed to streptococcal infections, Davis and Schmidt[7] found that 900,000 units of benzathine penicillin G given intramuscularly was effective in preventing streptococcal infections for a period of approximately twenty-one days. The reaction rate they observed was about 1 per cent.

Although we observed no urticarial-like reaction in any child receiving the intramuscular injection of benzathine penicillin G in this series, we did see hives twice among 100 children so treated at another time.[1] Thus, the reaction rates we observed in those getting oral or intramuscular benzathine penicillin G are both in fair agreement with those observed by others.

It would therefore appear that intramuscular and oral benzathine penicillin G are both effective in combating streptococcal infection. If the dose of oral medication is sufficiently large and given for ten days, there is little difference between it and 600,000 units of benzathine penicillin intramuscularly, although the latter may be somewhat more effective. Urticarial reactions from either the oral or the intramuscular route should be under 2 per cent with the doses used. Furthermore, for practical purposes, the difference between the reaction rates observed in those receiving intramuscular or oral penicillin is insignificant.

SUMMARY AND CONCLUSIONS

Intramuscular and oral benzathine penicillin G were compared as methods of therapy for beta hemolytic streptococcal infections in children.

In children under 4, a liquid preparation of benzathine penicillin G (Bicillin suspension) given in a total dose of 3,600,000 units in eight days, and, in older children, pills of benzathine penicillin G (Bicillin tablets) given in a total dose of 8,000,000 units in ten days appear to be almost as effective in preventing bacteriologic relapses as a single intramuscular dose of 600,000 units of benzathine penicillin G (Bicillin injection). Allergic reactions (urticaria) occurred in less than 1 per cent of the whole series.

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THE EARLY DIAGNOSIS OF PATENT DUCTUS ARTERIOSUS

LESLIE M. HOLVE, M.D., AND FORREST H. ADAMS, M.D.
LOS ANGELES, CALIF.

IN THE past several years many advances have been made in the fields of pediatric cardiology and cardiac surgery. Children can now be diagnosed and treated safely at earlier ages, even during the first few months of life.[1, 2]

With the aid of special diagnostic procedures, it has been shown that a number of infants and small children have surgically amenable lesions but do not have the classical findings such as seen in the older child and adult. This is especially true of the small child, but also occurs in the older child with a large left-to-right shunt due to a patent ductus arteriosus. Since these children frequently have cardiorespiratory difficulties at an early age and may die if misdiagnosed or untreated, special diagnostic studies should be done as soon as possible. It is only through these improved diagnostic modalities that needless morbidity and mortality can be reduced.

The purpose of this paper is to present data on a group of infants with large left-to-right shunts due to a patent ductus arteriosus and to emphasize the need and safety of doing specialized diagnostic studies and corrective surgery early, in selected cases.

From the Department of Pediatrics, School of Medicine, University of California at Los Angeles.

Presented before the Pediatric Section meeting of the Los Angeles County Medical Association, May 10, 1956.

During the year 1955 we had the opportunity of seeing six patients with the diagnosis of atypical patent ductus arteriosus; five were seen at the University Hospital, one was seen at the United States Naval Hospital in San Diego, California. All children were less than 2½ years of age, and four were less than 1 year of age. The clinical data on these patients have been summarized briefly in Table I.

CASE REPORTS

The following cases are described in detail to illustrate certain points.

CASE 1.—D. M., a 5-week-old Caucasian male, was admitted to the United States Naval Hospital, San Diego, because he "turned blue and quit breathing."

He was the product of a normal pregnancy and an uncomplicated delivery. The birth weight was 2.7 kilograms. No cyanosis was noted at birth. Because of rapid respirations, feeding the baby was difficult and the weight gain was quite poor. Following the episode of cyanosis and apnea, the patient was admitted to the hospital for evaluation.

The patient was a poorly nourished, pallid infant weighing 2.8 kilograms. He was in moderate respiratory distress and distention of the scalp and neck veins was noted. The pulse was 168 per minute. The lungs were clear to percussion and auscultation. The left border of cardiac dullness extended to the anterior axillary line in

the sixth intercostal space. A palpable systolic thrill was present over the cephalic portion of the sternum, and a harsh Grade 4 systolic murmur was heard over the entire precordium but best heard in the second left intercostal space adjacent to the sternum. A questionable, soft Grade 1 diastolic murmur was heard in the aortic area. The abdomen was soft and the liver was palpable at the right costal margin. The peripheral pulses were strong and easily palpable. No edema was present.

Routine blood work and urinalysis were within normal limits.

Roentgenographic studies revealed generalized cardiac enlargement involving both chambers and markedly increased pulmonary vascular markings.

The electrocardiogram was interpreted as showing sinus tachycardia and right ventricular hypertrophy.

TABLE I. CLINICAL DATA OF SIX CHILDREN WITH ATYPICAL PATENT DUCTUS ARTERIOSUS

CASE	AGE (MO.)	SEX	SYMPTOMS	CARDIAC FINDINGS	X-RAY	ECG	SPECIAL STUDIES	DISPOSITION
1	1¼	M	Poor growth Tachypnea Cyanosis	Systolic murmur, LSB ? Diastolic murmur Systolic thrill	4 + CE 3 + LM 3 + PA 3 + RV	RVH	0	Died
2	3	M	Tachypnea Subcostal retraction	Systolic murmur, LSB ? Diastolic murmur ↑ Pulse pressure	2 + CE 3 + LM 2 + PA 2 + LV	RVH LVH	Retrograde aortography	Surgery
3	3	M	Tachypnea Cyanosis Vomiting	Systolic murmur, LSB Diastolic murmur ↑ Pulse pressure	1 + CE 2 + LM 1 + PA 2 + LV	RVH LVH	Cardiac catheterization	Surgery
4	8	F	Poor growth Tachypnea Frequent infections	Systolic murmur, LSB Systolic thrill ↑ Pulse pressure	3 + CE 3 + LM 3 + PA 2 + RV 2 + LV	RVH LVH	Cardiac catheterization	Surgery
5	15	F	Tachypnea	Machinery murmur, LSB ↑ Pulse pressure	1 + CE 2 + LV	LVH	0	Surgery
6	30	F	Poor growth Frequent infections Irritability	Systolic murmur, LSB Diastolic murmur ↑ Pulse pressure	2 + CE 3 + LM 3 + PA 2 + RV	RVH	Cardiac catheterization	Surgery

CE=Cardiac enlargement
LM=Lung markings
PA=Pulmonary artery
RV=Right ventricle
LV=Left ventricle
LSB=Left sternal border
RVH=Right ventricular hypertrophy
LVH=Left ventricular hypertrophy

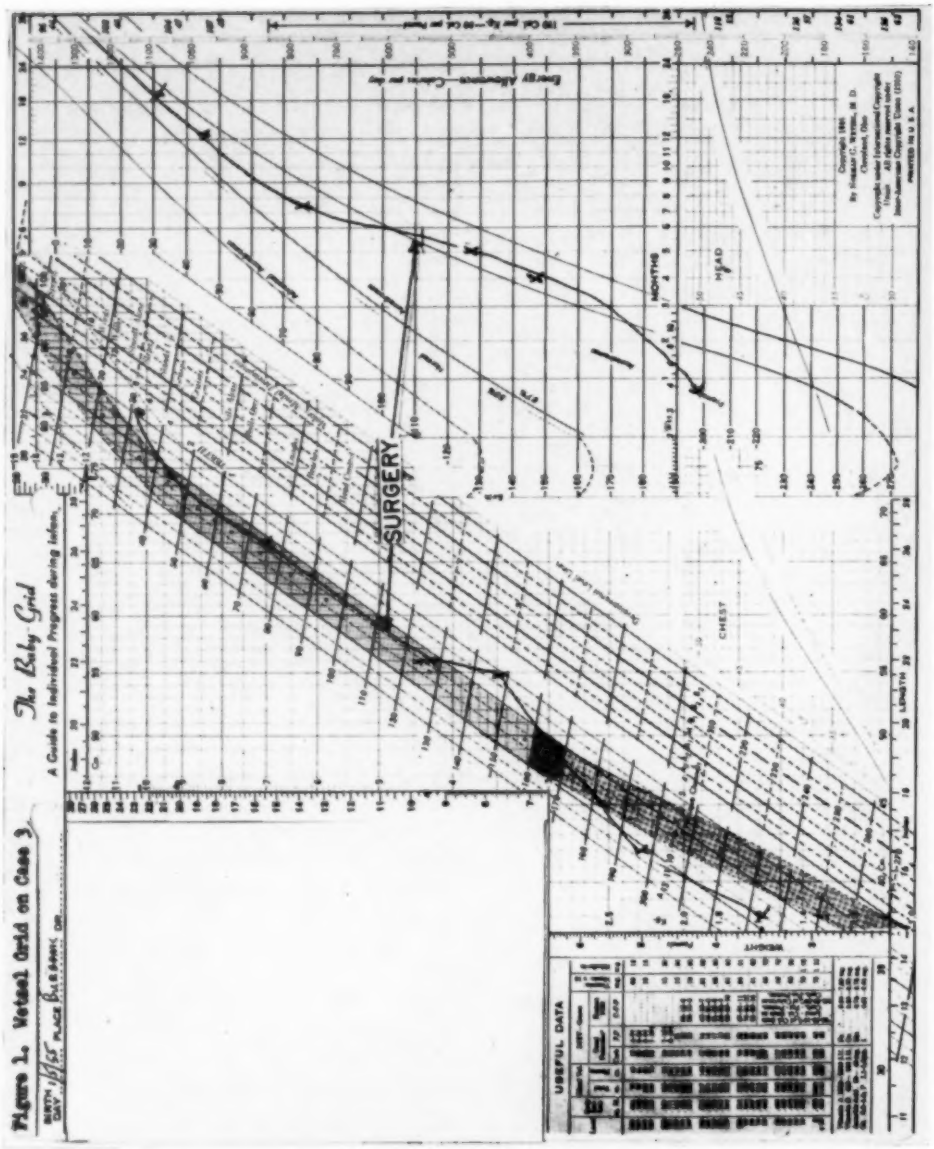
The Baby Grid
A Guide to Individual Progress during Infancy
SURGERY
USEFUL DATA
HEAD
CHEST
LENGTH
WEIGHT
MONTHS

Fig. 1.

Clinical impression: Interventricular septal defect versus a patent ductus arteriosus.

The child's course in the hospital was very poor. In spite of digitalization and antibiotic therapy the child developed progressive, intractable, congestive failure and repeated respiratory infections. Although cardiac catheterization was considered, it was not done because of the "danger" of the procedure.

Two months after the entry of the patient, he died in cardiorespiratory failure. At post-mortem examination a large patent ductus arteriosus, unaccompanied by other cardiac anomalies, was found.

CASE 3.—B. H., a 3-month-old Caucasian male, was referred to the University Hospital because of a heart murmur. He was the product of a twin pregnancy which was complicated by premature delivery after 6¾ months' gestation. Difficulty in resuscitation was encountered and the child remained in an Isolette for two weeks. It was not known if cyanosis was present at birth. No murmurs were heard in the neonatal period.

At 3 weeks of age rapid, heaving respirations were noted, and during the second month of life there were almost daily episodes of emesis. On several occasions cyanosis lasting five minutes occurred with these bouts of emesis. A murmur was heard for the first time at 7 weeks of age and he was referred to this hospital for evaluation and management.

The patient was a well-developed, well-nourished, pale, 3-month-old Caucasian male who had rapid respirations and a weak cry. No cyanosis was present. The pulse was 180 per minute. The blood pressure was 100/?. The lungs were clear to percussion and auscultation, and the heart was not enlarged. A loud, harsh, Grade 3 systolic murmur was heard over the entire precordium. Also a faint diastolic component was heard in the pulmonic area. The peripheral pulses were strong and easily palpable. The abdomen was rounded and soft; the liver was not palpable. No edema was present.

Routine blood work revealed a moderate anemia (hemoglobin, 8.4 grams) and a moderate leukocytosis with a normal differential for the age. The urinalysis was normal.

Roentgenographic studies revealed moderate, generalized cardiac enlargement and an increase in bronchovascular markings.

The electrocardiogram was interpreted as demonstrating normal axis deviation with combined hypertrophy.

Clinical impression: Patent ductus arteriosus; rule out interventricular septal or an interatrial septal defect.

The patient was observed in the Cardiac Clinic over a two-month period, with evidence of increasing cardiomegaly, pulmonary vascularity, and respiratory rate. A decreasing growth rate was apparent on the Wetzel Grid (Fig. 1). Cardiac catheterization was performed and confirmed the diagnosis of patent ductus arteriosus. The patient was explored through a left thoracotomy wound by Dr. William Longmire, Jr., and the ductus was ligated. The postoperative course was not complicated and the child was discharged one week after surgery.

Following the operation there was a rapid decrease of all previous symptoms and three months later the heart size was considered to be within normal limits, according to x-ray. Growth and development spurted (Fig. 1) postoperatively, and at 13 months of age both were normal. Nine months after operation only a Grade 1 soft systolic murmur could be heard along the left sternal border.

CASE 4.—P. L., an 8-month-old Negro female infant, was referred to the Medical Center for evaluation of her cardiac status. She was the product of an uncomplicated pregnancy and delivery. Her birth weight was 3.54 kilograms. No cyanosis or heart murmurs were noted at birth.

During the first three months of life, the patient had "frequent colds," poor

weight gain, and feeding difficulties. At 3 months of age, when the baby had her first bout of pneumonia, a harsh Grade 3 systolic murmur was heard for the first time. Cardiomegaly was also present. Subsequently, the patient developed pneumonitis on two separate occasions. Congestive failure occurred following the second episode of bronchopneumonia. Because of chronic cardiac failure, the patient remained in another hospital for approximately seven weeks before being transferred to the University Hospital.

The patient was a poorly nourished, pallid, lethargic, 8-month-old Negro female with rapid, labored respirations, weighing 5.5 kilograms. The pulse was 145 per minute. The blood pressure, taken by the flush technique, was 100 in the left arm and 115 in the left leg. There was an increase in breath sounds bilaterally; many rhonchi were heard over the left chest posteriorly. The left border of cardiac dullness extended to the anterior axillary line in the sixth intercostal space. A strong systolic thrill was palpable in the fourth and fifth intercostal spaces. Also a Grade 4 harsh systolic murmur was heard best along the left sternal border in the fourth and fifth intercostal spaces. The peripheral pulses were strong and easily palpable. The abdomen was rounded and soft; the liver was palpable 2 cm. below the right costal margin.

Roentgenographic examination revealed generalized cardiac enlargement with pulmonary plethora.

The electrocardiogram was interpreted as normal axis deviation with combined hypertrophy.

Clinical impression: Patent ductus arteriosus versus an interventricular septal defect, or both anomalies.

Cardiac catheterization was accomplished without difficulty, confirming the diagnosis of patent ductus arteriosus unaccompanied by other cardiac anomalies. The patient was operated upon by Dr. James Maloney, and a large patent ductus arteriosus (approximately the size of the aorta) was ligated. The postoperative course was uneventful. The child was discharged from the hospital eight days after the operation, greatly improved.

DISCUSSION

The clinical syndrome presented by patients with an atypical patent ductus arteriosus has been stressed recently by many authors.[3-8] The usual findings were failure to grow and develop normally, tachypnea, dyspnea, repeated respiratory infections, and easy fatigability. A wide pulse pressure was often present. Usually there was a harsh systolic murmur along the left sternal border and commonly a short diastolic component could also be distinguished. Cardiac enlargement of varying degrees was seen in all cases. The electrocardiograms revealed no consistent pattern.

The three cases were selected because they were considered to demonstrate clearly the value and urgent need of early diagnosis and therapy.

Case 1 illustrates vividly the necessity of establishing early and accurate diagnosis by special modalities. Had this been done, there is every reason to believe that this child's disorder could have been managed successfully through surgery and he could have been cured.

Case 4 represents another aspect of the problem. Because of the attempts to manage the case medically, without a clear-cut diagnosis, this girl's life was constantly threatened and needless morbidity sustained. Specific diagnosis by cardiac catheterization or aortography would have decided the course immediately and curative surgery could have been accomplished without any undue increase in risk.

Case 3 represents the type of patient management which approaches the

ideal. Early, the diagnosis of a cardiac lesion was suspected. When evidence of an adverse clinical course was obvious, special studies indicated the presence of an operable lesion. Surgical correction quickly followed. The postoperative course and follow-up data demonstrate the safety and satisfactory response to early closure of a patent ductus arteriosus in an infant with symptoms.

During early childhood, patent ductus arteriosus has frequently been considered to be a relatively benign cardiac anomaly.[9-12] That this is not always true has been verified by Abbott,[13] who reported twenty deaths in infants or children less than 5 years of age, among a total of ninety-two patients dying with uncomplicated patent ductus arteriosus. Other authors[3, 5-8] report lower but significant mortality rates for this lesion during infancy and early childhood.

Keith and Forsyth,[14] Zeigler,[3] Dammann and Sell,[5] Adams and co-workers,[6] Lyon and Kaplan,[7] and Ash and Fischer[8] have all emphasized that the diagnosis of patent ductus arteriosus can be made in the absence of the typical "machinery" murmur by special diagnostic studies—cardiac catheterization or retrograde aortography. The safety of such diagnostic procedures has been repeatedly demonstrated. When the physician is armed with an accurate diagnosis, surgical intervention and cure can be given to this group of patients at almost any age without unduly increasing their mortality risk. Gross and Langino[12] in 1951 achieved an over-all mortality rate of 2.1 per cent for all patients operated upon for patent ductus arteriosus and a mortality rate of 0.5 per cent for all patients who had no complications. Relatively few of Gross's patients were in the infancy age period. Zeigler[3] and Adams and associates[6] report in their series mortality rates of 5 and 6 per cent. There were no deaths among the patients who were operated upon, in the cases reported here.

SUMMARY

Patients with an atypical patent ductus arteriosus can be identified and treated safely during infancy with the aid of the special diagnostic modalities of cardiac catheterization and retrograde aortography. The clinical syndrome of tachypnea, dyspnea, repeated respiratory infections, easy fatigability and growth failure presented by these children has been described, and the summaries of six cases seen by us have been presented. Three patients were described in detail, to illustrate specific points and to demonstrate clearly the value of early diagnosis and treatment.

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Parents are often heard to complain of the obstinacy of their infants and the necessity of severe measures to reduce them to obedience. In a large number of instances the obstinacy of the child is either imaginary or the result of the parent's own mismanagement; and the severe means used to conquer it, in many cases, tend to confirm it while they act prejudicially upon the health of the little sufferer. The young infant is often reputed obstinate, because it cannot conform its wants to the convenience or the caprice of its parents; because it will not close its eyes in sleep at their desire—refrain from crying for food when it is hungry, and the mother is not ready to attend to its wants; or, when it begins to prattle, to form articulate sounds, at her command, to the pronunciation of which its organs of speech are not yet adapted. When the child is somewhat older, he is, perhaps, commanded to remain within doors, and sit still and study his lesson, while perhaps the gladsome sound of his companions' sports strike on his ear, and stimulate his desire to partake of them, or while he beholds, from his chamber, their gambols in the neighboring fields; under such circumstances, he can neither fix his mind upon his book, or remain quiescent for any length of time, however repeatedly he may be commanded to do so. The child evinces neither obstinacy nor disobedience; he is merely following the natural instinct of his age for bodily action; and if an attempt be made to restrain this by punishment, the mind and the temper as well as the health of the body, equally suffer injury.

D. Francis Condie: On the Diseases of Children, 1871.

TETANUS

General Considerations on 1,047 Cases Admitted to the Hospital das Clínicas de São Paulo

Dácio Pinheiro, M.D.
São Paulo, Brazil

TETANUS is a noncontagious infectious disease caused by action of the toxin produced by *Clostridium tetani* on the motor cells of the nervous system.

It is a disease known since Hippocrates, who stated: "The tetanic patient who goes through the fourth day of the disease will survive." Nicolaier, in 1885, produced the disease in experimental animals by the inoculation of garden soil. Noticing that the bacilli continued encapsulated, he suggested the possibility of a toxin being responsible for the symptomatology of the disease. Kitasato, in 1889, discovered the toxin and developed the antitoxin.

The etiological agent of tetanus, *Clostridium tetani,* is a sporulated bacillus, resembling the shape of a match. As it is an anaerobe, under adverse conditions it assumes the sporulated form protecting it against light and heat and enabling it to survive for more than ten years. The bacilli, as well as the spore, are widely distributed in nature, predominating, however, in certain areas.

Wounds, especially if deep and contaminated by clothes or earth, are the main sources of infection. Contaminated splinters are common causes in children. The bacilli probably enter the wound in the spore form and, finding favorable conditions, turn into the vegetative form, producing a strong toxin. The toxin is water-soluble and composed of two fractions: (1) tetanolysin without clinical significance and (2) tetanospasmin, which, through ways not yet established, reaches the central nervous system. At present the theory generally held is that of propagation along nervous pathways. When tetanospasmin becomes fixed to the ganglionic cells of the anterior horns of the medulla and the motor cranial nerves, it renders the nervous system easily excitable, and even the slightest stimuli start dangerous spasms or tetanic convulsions. On the other hand, the characteristic muscular hypertonia is produced by a peripheral action of the toxin on the myoneural junction.

According to the majority of authors, the incubation period of the disease varies from one to three weeks as a general rule. The figures obtained in a study carried out at the Hospital das Clínicas[20] in regard to the relation of the incubation period to mortality are given in Table I.

Analysis of Table I indicates that the mortality rate is higher in the

Da Clínica Pediátrica (responsável pelo Grupo de Tétano) da Fac. de Medicina da Universidade de São Paulo.

group with an incubation period of 1 to 5 days. This is explained by knowledge that short incubation periods correspond to the presence of extremely virulent bacilli and to large amounts of strong toxin, which are the elements responsible for the rapid toxic impregnation of the nervous system.

In Table II, based on the study, we have related the "onset time" with the mortality rate. "Onset time" means the period from the appearance of the first symptom to the first spasm. Cole first emphasized such "time," since the wounding and the contamination are not always chronologically coincident. The "onset time" gives a more accurate and valuable index of prognosis. An "onset time" shorter than 48 hours indicates a bad prognosis and in such cases, according to Cole, the period of survival of the tetanic patient is roughly three times the "onset time." Further, according to Cole, "onset time" shorter than 48 hours is only observed when one or more lethal doses are fixed in the central nervous system.

It can be seen that a higher mortality rate was observed in the group having an "onset time" shorter than 48 hours.

The first symptoms of tetanus must be recognized as early as possible, owing to the importance of the time element in the administration of the specific treatment. This may be difficult, especially in children, as the wounds are often not severe, or are not observed because they rapidly heal. For practical purposes it can be said that the symptomatology of tetanus consists essentially of generalized muscular hypertonia accompanied by continuous or intermittent spasms due to exaggerated reflex excitability. The clinical signs may vary from slight rigidity of some muscles to accentuated hypertonia of all voluntary muscles, giving the patient a characteristic aspect (i.e., trismus, risus sardonicus, opisthotonos, rigidity of the abdominal musculature, etc.). In Table III are computed the first symptoms of the disease and the incidence for 200 patients treated at the Hospital das Clínicas.[20]

Trismus is clearly the prevailing symptom. Indeed, "lockjaw" is a synonym for tetanus. The asphyxiating spasms of the respiratory and laryngeal musculature may cause death if not rapidly diagnosed and treated.

It must be emphasized that there is practically no rise of temperature in

TABLE I. RELATION BETWEEN THE INCUBATION PERIOD AND MORTALITY RATE

DAYS	NUMBER OF CASES	CURES	DEATHS	
			BEFORE 48 HR.	AFTER 48 HR.
1 to 5	19	8 (42.1%)	4 (21.0%)	7 (36.0%)
6 to 10	56	30 (53.5%)	11 (19.6%)	15 (26.7%)
More than 11	69	51 (73.9%)	6 (8.6%)	12 (17.3%)
No information	56	42	7	7

TABLE II. RELATION BETWEEN "ONSET TIME" AND MORTALITY RATE

"ONSET TIME" (DAYS)	CURES	DEATHS	
		BEFORE 48 HR.	AFTER 48 HR.
1 to 2	55	22	32
3 to 5	28	0	3
More than 6	17	1	1
No information	20	3	5
With no spasms	11	2	0

TABLE III. INITIAL SYMPTOMATOLOGY OF TETANUS

FIRST SYMPTOM	NUMBER OF TIMES OBSERVED
Trismus	111
Pain in back	40
Rigidity of neck	25
Pain in leg	14
No information	14
Generalized hypertonia	10
Dysphagia	9
Fever	9
Spasms	7
Poorly localized pain	2
Palpebral ptosis	2
Hypertonia of arm	1
Mental confusion	1
Cephalalgia	1
Dyspnea	1

tetanus; fever means a bad prognosis. There is also only slight alteration of the pulse rate. Its modification means guarded prognosis. The observation of accentuated tachycardia, even under the action of muscle-relaxing drugs, may be looked upon as a sign of exhaustion.

The mentality in tetanus remains unimpaired, the tetanic patient watching the dramatic evolution of his disease.

Tetanus may assume the clinical form of localized tetanus (characterized by rigidity and spasms of the musculature around the wound) or of generalized tetanus.

The most common complications are those of the respiratory tract, mainly pneumonopathies (atelectasis and bronchopneumonia), sepsis, and deformities of the dorsal vertebrae, especially in children.

DIAGNOSIS

Diagnosis of tetanus is not difficult when there is a recent history of a wound and characteristic clinical symptomatology. On the other hand, differential diagnosis must be made concerning other diseases that cause hyperexcitability of the central nervous system. Among these are the following:

Meningitis.—The outstanding symptoms in differential diagnosis are disturbance of sensorium, high fever, vomiting, exaggeration of reflexes (hyperreflexia), and changes in the cerebrospinal fluid.

Hydrophobia.—The differential diagnosis is based on the history of bite by a suspected dog and a clinical picture in which the spasms are limited to the respiratory and swallowing musculature.

Strychnine Poisoning.—Such poisoning is due to accidental or intentional ingestion of the drug, absence of suspected wound, and muscular relaxation between crises of convulsions.

Tetany.—In tetany the spasms are characteristically located in the muscles of the feet and hands. In children, it is usually observed between 6 and 24 months of age. If in doubt, determination of serum calcium will reveal a low level.

Local Causes of Trismus and Dysphagia.—Peritonsillar abscess, epidemic parotiditis, throat infection, alveolar abscess, etc., may produce trismus, but not the other manifestations of tetanus.

Causes of Convulsions and Tetany in the Newborn Infant.—Birth injuries to the brain (intracranial hemorrhage, cerebral edema, anoxia), congenital cerebral defect, alkalosis, hypoglycemia, kernicterus, sepsis, excessive use of stimulant drugs to resuscitate the baby, and fever, may at times simulate tetanus.

PROGNOSIS

The prognosis of tetanus is always serious and unfavorable. Its mortality rate is still high (40 to 50 per cent) throughout the world. At present, the rate at the Hospital das Clinicas is 43.7 per cent. Mortality is influenced by and depends chiefly on the following factors:

1. Convulsions (if not controlled, may cause death).
2. Complications (chiefly those of the respiratory tract).
3. Short incubation period (less than 5 days).
4. "Onset time" shorter than 48 hours.
5. General condition of the patient aggravated by fever and tachycardia.
6. Nature of the wound, chiefly those produced by firearms, infected wounds, etc.
7. Age; deaths are most frequent among newborn patients.

CLASSIFICATION OF CASES

We classify cases of tetanus into three types, according to the conditions presented by the patients on admission:

Mild Tetanus.—

1. Incubation period longer than 6 days.
2. Interval between the first symptom and the first spasm longer than 5 days.
3. Infrequent and weak spasms.
4. No fever, or slight fever.
5. Good general condition.

Moderate Tetanus.—Frequent spasms, but no crisis of apnea or cyanosis. The same conditions as in mild tetanus are generally observed.

Severe Cases.—

1. Short incubation period (1 to 5 days).
2. Interval between the first symptom and the first spasm shorter than 5 days.
3. Frequent and strong spasms, accompanied by crisis of apnea and cyanosis.
4. Fever.
5. Complications of various kinds (pulmonary, circulatory, renal, etc.).
6. Elderly and newborn patients.

TREATMENT

Treatment of tetanus may be considered from two standpoints: (1) prophylactic and (2) curative.

Prophylactic Treatment.—The most important treatment for tetanus is preventive, considering the fact that tetanus is a serious disease with a high mortality rate. Active tetanus immunization should be carried out extensively. Educational campaigns should be developed to show the danger of accidents and the necessity of mass vaccination, particularly for those who are more exposed to the disease, such as children, soldiers, and farmers. Active immunization is quite practical and effective. This was proved once more during the Second World War, when the incidence of tetanus in wounded soldiers was minimal. In France, antitetanic vaccination is compulsory.

In children, active immunization is achieved after the third month of life by the intramuscular injection of three doses of 0.5 ml. of tetanus toxoid at monthly intervals. In this way, protective immunity is acquired for at least 12 months and probably much longer. A booster dose of 0.5 ml. of

toxoid should be repeated one year after completion of the basic immunization and at five-year intervals thereafter, or in the presence of any suspected wound. If a suspected wound occurs in children unvaccinated, the best prophylaxis is by combined immunization (i.e., administration of antitetanic serum, combined with 0.5 ml. of fluid tetanus toxoid).

The greatest problem in passive immunization is the frequent lack of an appropriate indication for use of the antitetanic serum. Since most wounds are not severe, they are not noticed and, therefore, no opportunity for prophylaxis occurs. On the other hand, if the patient is given repeated doses of tetanus antitoxin, he may become hypersensitive and the serum therapy may be dangerous. The dosage of antitetanic serum to be injected varies according to the nature of the wound, but for the less serious wounds it should never be less than 3,000 American units. This dosage, capable of immunizing the patient for ten days, should be repeated if the wound is still suspected to be infected, in order to prevent postserum tetanus.[20]

It should never be forgotten that proper surgical treatment of the suspected focus is also an important prophylactic measure. In cases of wounds contaminated chiefly by earth, and in cases in which there is an interval of some days between the injury and the administration of the antitoxin, it is recommended that a dose of 5,000 to 20,000 A.U. be given intramuscularly. The antitetanic serum should never be given before obtaining a careful allergic history and after testing for sensitivity to serum. In case of a positive or dubious test, the antitoxin is administered by subcutaneous and intramuscular route, according to the hyposensitization scheme of De Sanctis and Varga.[3] If available, tetanus antitoxin prepared from bovine serum may be given to those individuals sensitive to horse serum.

TABLE IV. RELATION ACCORDING TO AGE, NUMBER OF CASES, AND MORTALITY RATE

	NO. CASES	CURES	DEATHS	MORTALITY RATE
Adults	329	207	122	37%
Children (1-14 yr.)	462	293	138	29 (87%)
			31 (other causes)	
			169	
Newborn infants	256	40	198	77 (34%)
			18 (other causes)	
			216	

Curative Treatment.—In the past eleven and one-half years 1,047 patients with tetanus were admitted to the Hospital das Clínicas de São Paulo (Brasil), with the following distribution according to age, number of cases, and mortality (Table IV).

The figures in Table IV once again corroborate the fact that tetanus is much more common in children than it is in adults, and that the mortality rate is highest in tetanus of the newborn.

The most important objectives in the management of tetanus are as follows:

1. *Relaxation and sedation of the patient.* Deaths are nearly always

caused by convulsive asphyxia consequent to a tonic spasm of the respiratory musculature, or by exhaustion. The ideal sedative would be one that could produce rapid and deep relaxation with a minimal dose capable of abolishing the convulsion and hypertonia, but without loss of consciousness and with no respiratory depression. It should also have a low toxicity in order to allow its use in adequate doses. The introduction of 3-orthotoloxy-1,2-propanediol (Tolserol, Myanesin, or mephenesin) a nontoxic, muscle-relaxing drug that does not depress the respiratory center, offered great hope for the solution of this serious problem.

Veronesi and Meira,[21] in 1951, first used Tolserol in the treatment of tetanus in adults. At about the same time, we started employing the drug in our clinic to relax children and newborn babies hospitalized with tetanus. Results obtained with Tolserol in the management of infants with tetanus admitted to the Hospital das Clínicas have been most encouraging, and we have obtained better results with this drug than with any previous agents.

2. *Serotherapy* to neutralize and prevent new doses of toxin from reaching the nervous system.

3. *Débridement* of the suspected focus to stop the production of toxin.

4. *Symptomatic and general care.* Here are grouped a certain number of important measures that are normally carried out in the treatment of any patient with tetanus. Special emphasis is given to the value of constant, day and night, watchful nursing.

Before considering in detail our therapeutic schedule, it would be useful to emphasize that, considering the severity of the disease, a rigid and immutable standardization cannot be followed in the management of tetanus. *Treatment must be individualized according to the particular conditions of each case.* Nevertheless, the following therapeutic schedule is the one that has given the best results and for this reason we recommend it.

SEVERE CASES

I. TETANUS NEONATORUM

1. *Muscular relaxation and sedation.* THE FIRST AND MOST URGENT STEP TO BE CARRIED OUT IS TO RELAX AND SEDATE THE TETANIC PATIENT.

Initial dose: 5 ml. of 2 per cent Tolserol intravenously at the rate of 1 ml. per minute. Complete relaxation is usually observed immediately following administration of the drug.

Daily maintenance dose during the first week: 100 to 150 ml. of 2 per cent solution of Tolserol, i.e., 2 to 3 Gm. of Tolserol, according to individual necessities, to be diluted into the whole amount of fluid (saline, glucose, etc.) that the patient will receive intravenously during each 24 hours of treatment. We recommend dissection of the external saphenous vein and the introduction of a polyethylene tube in order to facilitate the administration of the drug by continuous intravenous drip.

Daily maintenance dose from the eighth to the twenty-first day: After the first week the patient may begin oral intake. It will then be possible to discontinue the intravenous administration of Tolserol and start employing the rectal route. Our experience in this respect has shown that usually the newborn infant does not accept Tolserol very well by mouth, even when it is sweetened or diluted in juices or syrups. The application of a nasal

catheter in this stage of the illness will become a permanent and powerful source of spasms. For this reason we have, for some time, abandoned the administration of Tolserol in tablets and elixir. We decided upon the idea of administering Tolserol rectally, a practice which we have been utilizing for some time with excellent success. The Tolserol suppository contains 1 Gm. of the drug and daily doses vary from 6 to 12 Gm., according to the individual patient's need. This is divided into doses administered every 2, 3, or 4 hours. With the lessening of the hypertonia the dosage may be progressively diminished, so that by the end of the second or third week the drug is discontinued.

2. *Serotherapy.* 60,000 A.U. of antitetanic serum is given intravenously after negative tests for sensitivity. In order to render the administration easier and to avoid disagreeable accidents, the serum is diluted into the whole amount of glucose that the patient will receive by intravenous drip for his nutrition.

3. *Débridement of the focus.* We employ débridement and surgical cleansing of the umbilical wound, when necessary, with local infiltration of 10,000 A.U. antitetanic serum and 100,000 A.U. of crystalline penicillin after previous novocainization. Omphalectomy is still a debated indication. At present, we are practicing it in some of our cases. Such surgical treatment should obviously be carried out after the administration of antitetanic serum intravenously, and with the patient well sedated.

4. *Symptomatic and general care.* Since these measures are applied in all cases of tetanus, they are mentioned here but not repeated later.

   a. A most important aspect of treatment is permanent vigilance by trained nurses, interns, and residents to that they will be able to assist the patient at any time, especially in cases of emergency. Permanent assistance to every patient is of the utmost importance. TREATMENT WILL BE TRUSTWORTHY ONLY WITH CONSTANT 24-HOUR VIGILANCE TO ASSIST THE TETANIC PATIENT IN ANY CASE OF NECESSITY. A patient apparently well may have a severe spasm caused by a small stimulus (light, noise, etc.) and die in apnea if not immediately assisted. The tetanic patient should never be left alone during the first stages of the disease if the doctor does not want to run the risk of finding him dead on returning to his room. The medical literature points out, and we have many examples confirmatory, that survival of the patient was due chiefly to excellent nursing assistance.

   b. Periodical observation of vital signs (temperature, pulse, and respiratory rate).

   Isolation in a dark and silent room, limiting his manipulation to the minimum.

   d. We advise the Trendelenburg position if there is accumulation of secretions in the bronchial tree. We try to keep the respiratory tract clean either by:

      (1) Aspiration of the oropharynx, when necessary, or

      (2) Tracheotomy when indicated. In contradiction to the opinion of many authors, we do not favor tracheotomy as a routine procedure and rarely practice it. This intervention should be recommended only when there is evident spasm of the larynx or when the accumulation of secretion hinders its aspiration.[20]

   e. Oxygen by tent or funnel, when indicated.

   g. Periodical control of the functional conditions of the resuscitator which may be needed at times.

   h. Keep near the patient's bed all of the necessary emergency material, including proper instruments for tracheotomy.

   i. Periodical change of posture to prevent decubitus ulcer and pulmonary stasis.

j. Urethral catherization when needed.

k. Daily penicillin, associated, when indicated, with other antibiotics.

l. Administration of antihistaminics to prevent allergic incidents.

m. Prescribe special oral or parenteral diet (PARENTAL INTRAVENOUS NOURISHMENT IS ABSOLUTELY NECESSARY DURING THE FIRST WEEK) to maintain and correct, when necessary, the water and electrolyte balance of nutrition.

n. Administration of blood or plasma when indicated.

o. Physiotherapy treatment (tepid baths, muscular exercises and massages, etc.) is started immediately after cessation of spasms.

p. Active immunization is started in 30 days.

q. In case of a crisis of apnea, proceed in the following way:

(1) Try to relax the musculature involved as fast as possible with Tolserol given intravenously in the required dose to abolish the spasm.

(2) While waiting for the effect of the injection, start artificial respiration.

(3) Increase the maintenance dose of the muscular relaxant in order to avoid more crises.

II. ADULTS AND CHILDREN (more than 1 year of age)

1. *Muscular relaxation and sedation.*

Initial dose: 10 to 20 ml. of 2 per cent Tolserol intravenously at the rate of 1 ml. per minute.

Daily maintenance dose during the first week: 6 to 18 Gm. of Tolserol, according to the needs of each case, diluted in the whole amount of fluid that will be given to the patient during the next 24 hours by the drip method in order to maintain his general condition. This solution should be previously warmed in a water bath.

Daily maintenance dose from the eighth to the twenty-first day: Considering that after the first week the patient may begin oral intake, it will be possible to stop the intravenous administration of Tolserol and use the oral or rectal route. Daily doses vary, according to the age and needs of each patient, from 12 to 24 Gm., in divided doses administered at intervals of 2, 3, or 4 hours. In view of the large variation of the doses, the physician must adjust the dose to the best of his ability, according to the individual patient's response. With the lessening of hypertonia, this dosage may be progressively reduced, and at the end of the second or third week the administration of Tolserol may be discontinued.

2. *Serotherapy.* Experiments with human beings and animals have proved that the following doses, which we have been employing for a long time with success, are quite sufficient: for children, 60,000 A.U. of antitetanic serum; for adults, 100,000 A.U. antitetanic serum. In children we have proceeded as previously described, while to adults we give half the dose intravenously and the other half intramuscularly after negative ophthalmic and intradermal tests for sensitivity. If the tests show a positive or dubious result, the serum is administered according to the Bersredka method of desensitization, only by subcutaneous and intramuscular routes.

3. *Débridement of the focus.* The surgical treatment of the suspected focus consists of wide excision of the wound to establish aerobic conditions, cleansing with oxidizing liquids, etc. Our statistical data reveal that in patients in whom there is débridement the mortality rate is lower (29.8 per cent) than in those without débridement (37.3 per cent). For obvious reasons débridement should be practiced only when the patient is under the action of a sedative and after the administration of antitetanic serum. Previous local infiltration with antitetanic serum and crystalline penicillin is desirable.

4. *Symptomatic and general care.* See paragraph 4 in the section dealing with treatment of tetanus neonatorum.

MILD AND MODERATE TETANUS

1. *Muscular relaxation and sedation.* Generally speaking, these patients do not urgently require muscular relaxation or immediate sedation. These effects may be easily obtained through the oral or rectal route. The doses of Tolserol are the same as indicated previously, but the physician must adapt them to individual needs.
2. *Serotherapy.* (See previous discussion.)
3. *Débridement of the focus.* (See previous discussion.)
4. *Symptomatic and general care.* (See previous discussion.)

Table V indicates the superiority of this new treatment plan. These figures indicate that the therapeutic schedule now in use has brought to our statis-

TABLE V. RELATION BETWEEN THERAPEUTIC SCHEDULE AND MORTALITY RATE

	NO. CASES (ADULTS AND CHILDREN*)	CURES	DEATHS
Veronesi and Pinheiro schedule	181	138 (76.3%)	43 (23.7%)
Other schedules†	523	330 (63.1%)	193 (36.9%
Total	704	468 (66.4%)	236 (33.5%)

*Excluding tetanus neonatorum.

†Characterized mainly by using larger doses of antitetanic serum, various muscle relaxants, and sedatives, such as chloral hydrate, magnesium sulfate, barbiturates, etc.

ties an amelioration never before observed, and this improvement of 13.2 per cent in our mortality rate gives us one of the best and lowest tetanus lethality ratios in the world. Following the same plan, the mortality rate in our cases of umbilical tetanus dropped markedly from 92.5 to 77.3 per cent.

CONCLUSIONS

Some general considerations concerning tetanus and the results of my experience in the treatment of tetanus in children and adults with a new therapeutic schedule are presented. The most important therapeutic points are analyzed: (1) the value of a new muscle-relaxing drug (Tolserol, Myanesin, or mephenesin); (2) the antitetanic serum dose standardization; (3) the systematization of a certain number of collateral measures with special emphasis on the value of a twenty-four-hour vigilance by trained staff.

In eleven and one-half years, 1,047 patients with tetanus were admitted to the Hospital das Clínicas de São Paulo. The mortality rate, excluding tetanus neonatorum, dropped from 37.5 to 23.7 per cent with the introduction of the Veronesi and Pinheiro plan of treatment. This is one of the best and lowest mortality rates in the literature.

There were 256 patients with tetanus neonatorum among the 1,047 hospitalized. A detailed report on these cases will be published in another paper. With the adoption of the new plan of treatment, the mortality rate dropped 15.2 per cent in tetanus neonatorum.

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CHLORPROMAZINE IN PEDIATRIC SURGERY

A Clinical Report of 100 Cases

Fethi Tevetoğlu, M.D., and Joseph A. Abbey, M.D.
Corpus Christi, Texas

FOR several years reports have described the satisfactory results obtained with chlorpromazine in widely varied fields: anesthesia and surgery, psychiatry, pharmacology, obstetrics, gynecology, and pediatrics. In mid-1951 chlorpromazine was first used by Laborit and Huguenard[23] in producing artificial hibernation, and Laborit demonstrated its efficacy in anesthesia in combination with pethidine hydrochloride. Delay and Deniker[12] showed the drug to be a valuable aid in psychiatry in 1952. In the United States chlorpromazine was used first in 1953 by Smith and Fairer[39] in anesthesia, and in the production of hypothermia by surface cooling.[16]

The first application of chlorpromazine in pediatrics was described in 1952 by Chédid and Fargeallah[7] and by Sorel and co-workers,[40] who produced artificial hibernation in preagonal infants with pronounced neurotoxicity. The following year many other French investigators reported the use of the drug in the treatment of toxicosis[6, 29] and encephalitis[3, 23, 24] and in the control of vomiting in term and premature infants.[35] By late 1954 the drug had been put to other therapeutic uses in pediatric neurology: the treatment of convulsions, encephalitis, chorea, bulbar poliomyelitis, and aerodynia and of acute dyspepsia in nursing infants.[3, 14] Greninger and colleagues[22] reported the successful treatment of tetanus in two children, with chlorpromazine and serovaccine therapy. In Germany, Janssen and Wilms[25] treated encephalopathies and meningopathies with the drug.

Since 1954 chlorpromazine has been applied in other areas in pediatrics with excellent results: in cerebromeningeal complications or obstetrical trauma of term and premature infants,[4, 34-36] in hyperactive mentally retarded,[2, 17] in emotionally maladjusted children,[19, 20] and in cases of cerebral palsy.[13, 18] The drug has also been effective as an antiemetic[9, 11, 31, 33, 42, 45] in the treatment of pertussis.[37] It has been used successfully in treating tetanus,[8, 26, 27, 32, 41] tetanus neonatorum,[21] and eberthian infection.[38] Bleckman and Salus[5] put the drug to use in pediatric electroencephalography and pneumoencephalography with good results.

In pediatric anesthesia and surgery chlorpromazine has been used in a rather large series of patients undergoing ophthalmologic, orthopedic, plastic, and general surgical procedures. Following the studies of Alessandri and Negroni,[1] Walter[43]

From the Driscoll Foundation Children's Hospital.

used chlorpromazine to prepare children for tonsillectomies and endoscopic examinations. Martin and associates[30] pointed out that the addition of oral chlorpromazine to the usual preoperative medication made it possible to reduce the amount of ether used in tonsillectomies. Patients appeared to be much happier when they awoke and were less distressed by sore throats. The recent reviews of Dobkin and co-workers[15] and Cutright[10] and Weiss[44] were valuable in pointing out the effects of chlorpromazine premedication on anesthesia and on postanesthetic symptoms.

The reports of many investigators and the results of our previous experience have shown that chlorpromazine relieves nausea and vomiting, produces drowsiness—often to the point of sleep—and reduces oropharyngeal secretions. Although these effects can be annoying, they serve useful purposes in preparing children for surgery.

In addition to enhancing the sedative and analgesic properties of barbiturates and opiates, chlorpromazine potentiates the action of anesthetics. It was these properties of the drug that led us to further investigation of its usefulness in pediatric anesthesia and surgery.

METHOD

This study is based on observation of one hundred children who received chlorpromazine as preoperative medication at the Driscoll Foundation Children's Hospital. Ranging in age from 11 months to 14 years, the group comprised fifty-five males and forty-five females. Seventy-five were admitted for tonsillectomies and adenoidectomies, fifteen for general surgery, four for plastic procedures, four for orthopedic surgery, one for a pneumoencephalogram, and one for a laryngoscopy (Table I).

TABLE I. PATIENTS PREMEDICATED WITH CHLORPROMAZINE PRIOR TO GENERAL ANESTHESIA

OPERATION	NO. OF PATIENTS	AGE RANGE
Tonsillectomy, adenoidectomy	75	3-14 yr.
General surgery (herniorrhaphy, circumcision, appendectomy, incision of infected ingrowing toenail, excision of thyroglossal cyst, exploratory laparotomy)	15	11 mo.-14 yr.
Plastic repair (harelip, hypospadias, incision of cicatricial contracture of left axillary fold, and skin graft, burns)	4	1-12 yr.
Orthopedic (bone biopsies, open reduction)	4	2-14 yr.
Neurosurgery (pneumoencephalography)	1	5¼ yr.
Laryngology (laryngoscopy)	1	1½ yr.

In all cases atropine and Demerol were administered concomitantly with chlorpromazine as premedication. Generally, the chlorpromazine dosage was calculated on the basis of 0.5 mg. for each kilogram of body weight. Chlorpromazine was administered orally in ninety-six cases (two to three hours before operation), and by the intramuscular route in four cases (one-half to two hours before operation). Atropine and Demerol were administered subcutaneously fifteen minutes to one hour before surgery as follows: 11 months to 6 years of age (9 to 21 kilograms in body weight) $\frac{1}{350}$ to $\frac{1}{250}$ grain of atropine and 15 to 30 mg. of Demerol; 7 to 9 years of age (22 to 29 kilograms in body weight) $\frac{1}{250}$ to $\frac{1}{200}$ grain of atropine, and 35 to 45 mg. of

Demerol; 10 to 14 years of age (30 to 50 kilogram in body weight) 1/200 to 1/150 grain of atropine and 50 mg. of Demerol.

RESULTS

All patients who received chlorpromazine preoperatively—by either the oral or the intramuscular route—were calm and had a sense of well-being. Apprehension was markedly reduced. Prior to the administration of chlorpromazine, throughout the operative procedure, and for two to three hours postoperatively repeated blood pressure readings revealed no hypotensive effects of the drug in any patient. The period of induction of anesthesia was smoother and shorter, and less anesthetic was required.

Although we have not observed any severe side effects from the use of chlorpromazine along with other preanesthetic medications, there is still the possibility of hypotension as a result of the combined effects of these agents, which should be kept in mind for any patients requiring general anesthesia.

In tonsillectomies and adenoidectomies rapid relaxation of the jaw made insertion of the mouth gag and airway possible early in the operative procedure. Consequently, it was less often necessary to carry the patient to the surgical plane of anesthesia before his mouth could be opened. Furthermore, the anesthetist did not have to deal with the excessive oral and oropharyngeal secretions that normally make the induction of children difficult.

There was less bleeding during surgery, and the marked diminution—or even complete absence—of postoperative nausea was gratifying. Of the seventy-five tonsillectomy operations there was only one case of postoperative bleeding. This occurred one hour after surgery in a 13-year-old, obese girl; bleeding from the left tonsillar fossa and the base of the tongue was controlled by suturing. She was discharged after two days without further complications.

A large percentage of the patients were mildly drowsy for four to six hours and remained quiet in bed without the usual postoperative excitement. None required sedatives. Patients could be aroused easily and were able to take oral nourishment the same evening.

None of the four asthmatic children in the group suffered an attack of asthma between the time they received chlorpromazine and their re-examination one week after discharge from the hospital. Although this is seen as a rule in most postoperative cases, it was particularly noted that these children were totally and completely free of any lung symptoms. In two cases the calming effect of the drug made plastic repair of burns considerably less difficult.

SUMMARY

Chlorpromazine was administered as part of the preoperative medication given to one hundred children. Apprehension was markedly reduced and induction of anesthesia was easier in all cases. Furthermore, less anesthetic was required to produce adequate relaxation. There was some diminution of salivary secretions, and repeated blood pressure determinations revealed no hypotensive reactions in the group. Bleeding during surgery was reduced. Postoperative nausea and vomiting were almost completely eradicated,

and the recovery period was calmer. In the seventy-five tonsillectomy and adenoidectomy operations included there was almost complete elimination of the restlessness and apprehension usually following such surgery.

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Juvenile Delinquency—Two Hundred Years Ago

Whereas Complaint has been made to the Selectmen that the Children behave very unmannerly and indescently in the Streets and use bad Language, Voted that the Masters of the respective Schools in the Town be desired to reprove Said Children for such Misdemeanors.

MINUTES OF BOSTON SELECTMEN, January 19, 1757.

LOW CEREBROSPINAL FLUID GLUCOSE ASSOCIATED WITH MENINGEAL NEOPLASIA

WILLIAM T. DUNGAN, M.D., AND ROBERT M. MCKEY, JR., M.D.
NASHVILLE, TENN.

LOW cerebrospinal fluid sugar associated with diffuse neoplastic involvement of the leptomeninges has been reported in the neurological literature. Several cases have occurred in children.[1-4] Three such cases have been presented recently in reports of clinicopathological conferences.[4-6] The syndrome has received no emphasis in the pediatric literature.

CASE REPORT

A 4-year-old white male was admitted to Vanderbilt University Hospital on Feb. 5, 1956, because of headache. Family history revealed that a maternal great-uncle had died of tuberculosis, but there had been no contact. The patient was in good health until six weeks prior to admission, when he developed intermittent headache and vomiting, with increasing lethargy. One day prior to admission the referring physician detected strabismus and facial weakness. Temperature had remained normal.

Physical examination revealed a well-developed, well-nourished white male who was drowsy and irritable. The temperature was 98.8° F., pulse 66, respirations 22, and blood pressure 95/60. Pertinent findings were limited to the neurological examination. There was complete paralysis of the left abducens nerve and partial peripheral right seventh nerve weakness. Funduscopic examination was normal. There was slight motor weakness in the right leg. Deep tendon reflexes were sluggish but equal bilaterally. The Babinski response was flexor. There were no signs of meningeal irritation.

Urinalyses were negative. Complete blood counts revealed only a persistently increased erythrocyte sedimentation rate. Old tuberculin and histoplasmin skin tests were negative. X-rays of the skull and chest were normal. Serial examinations of the cerebrospinal fluid are summarized in Table I. The most striking finding was the consistently reduced sugar in the cerebrospinal fluid obtained from the lumbar subarachnoid space.

Admission diagnosis was intracranial neoplasm, probably a glioma of the brain stem. After the above studies, diagnoses of neoplasm, tuberculous meningitis and mycotic meningitis were considered. The long afebrile course and negative OT skin test made tuberculous meningitis unlikely. Repeated smears and cultures of the cerebrospinal fluid failed to reveal an infectious agent. India ink preparations and cultures on Sabouraud's media were negative for *Cryptococcus neoformans.*

The patient remained lethargic and vomited occasionally. Headache was a prominent complaint. A low-grade fever was present throughout the remainder of his illness. Papilledema was never present, nor was there evidence of meningeal irritation. On the eighth hospital day he had a generalized tonic-clonic convulsion. Ventricular air injection performed on the ninth hospital day revealed symmetrically dilated ventricles, with

From the Department of Pediatrics, Vanderbilt University School of Medicine.

TABLE I. SUMMARY OF CEREBROSPINAL FLUID EXAMINATIONS

DATE	SOURCE	APPEARANCE	PRESSURE (MM. CSF)	CELLS			PROTEIN (MG. %)	SUGAR (MG. %)	BLOOD SUGAR (MG. %)	CULTURES
				RBC	POLYS.	LYMPHS.				
2/ 5/56	Lumbar	Clear	240/140	0	4	7	18	10	62	No growth
2/ 7/56	Lumbar	Blood-tinged*	240/170	323	18	2	16	18	87	No growth
2/13/56	Lumbar	Blood-tinged*	230/—	504	7	4	46	15	74	No growth
2/14/56†	Ventricular	Clear	"Increased"	55	18	2	8	49		No growth
2/24/56	Ventricular	Clear	"Increased"				12	69		

*Traumatic taps.
†Receiving D_5W intravenously.

failure of the air to pass below the aqueduct of Sylvius. A posterior fossa craniotomy revealed thickened and opaque arachnoid over the cisterna magna and cerebellar hemispheres, suggesting chronic granulomatous meningitis. After a portion of the involved arachnoid had been taken for biopsy the wound was closed.

Because of the appearance of the leptomeninges at operation, antituberculous treatment was begun. This was discontinued when the biopsy revealed a chronic inflammatory reaction without evidence of tuberculosis. Smears and culture of ventricular fluid and the biopsy specimen were negative for bacteria and fungi. The protein and sugar contents of the ventricular fluid were normal; the patient was receiving intravenous dextrose when the first of these fluids was obtained. (See Table I.)

Postoperatively there was no improvement. On the tenth postoperative day a series of generalized convulsions was controlled by ventricular decompression through the operative site. The patient subsequently remained unresponsive and died several hours later.

Post-mortem examination was performed two and one-half hours after death. There was generalized thickening of the meninges. The lateral ventricles and aqueduct of Sylvius were symmetrically dilated. Nodules of tumor tissue were present in many areas of the cerebral cortex, at the corticomedullary junction, and in the cerebellum.

Microscopically there was generalized meningeal involvement by tumor and focal nodular infiltration of the brain substance. The tumor was composed of sheets of cells resembling glial elements with scanty basophilic cytoplasm and small vesicular nuclei exhibiting considerable pleomorphism. (Fig. 1.) Only rare mitoses were seen. Pathologically the tumor was thought to be a poorly differentiated glioma.

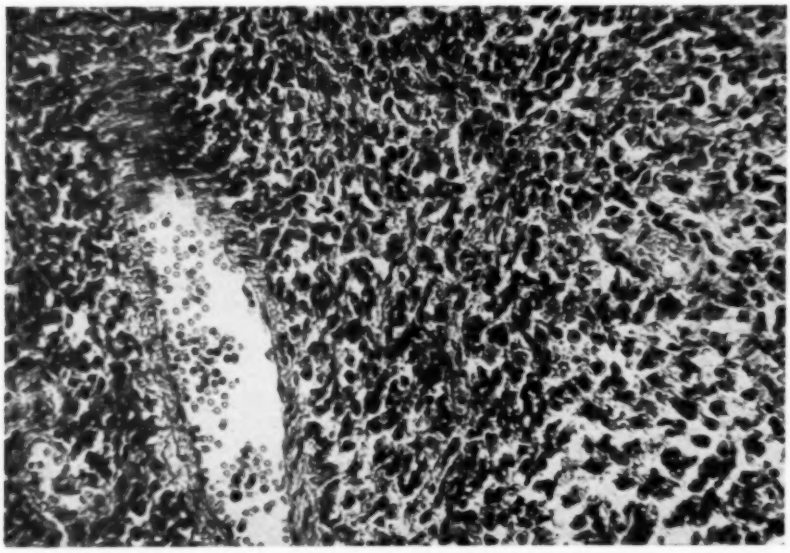

Fig. 1.

None of the tumor sites could be called definitely primary. It is possible that one of the tumor nodules

within the brain substance was primary and that the meningeal spread and the other intramedullary nodules represented metastases. However, it is quite possible that the primary focus of tumor was in the meninges, as extramedullary gliomas are known to arise from heterotopic glial tissue.[7]

COMMENT

The mechanism of production of low cerebrospinal fluid sugar in neoplastic meningitis has not been satisfactorily explained. This association was first recorded by Rindfleisch[8] in 1904. Berg[3] in 1953 summarized the published reports of hypoglycorrhachia of noninfectious origin and presented five additional cases. He stressed the importance of low cerebrospinal fluid sugar as a sign of diffuse meningeal tumor involvement when infection is unlikely. Hypoglycorrhachia was present in 75 per cent of the fifty-seven published cases of diffuse meningeal neoplasia.

A variety of neoplastic diseases may involve the leptomeninges and can be accompanied by an abnormally low cerebrospinal fluid sugar. Metastatic carcinoma, glioma, sarcoma, lymphoma, leukemia, and melanoma have caused this syndrome.[3] The most likely incorrect diagnosis of this condition in children would probably be tuberculous meningitis. Weighted clinical importance is attached to low cerebrospinal fluid glucose values in diagnosing infections of the leptomeninges. Diffuse meningeal neoplasia must be included in the differential diagnosis of central nervous system disease associated with reduced cerebrospinal fluid glucose, especially when no definite infectious etiology is established.

SUMMARY

A case of diffuse meningeal gliomatosis with hypoglycorrhachia in a 4-year-old child is presented.

Inclusion of this syndrome in the differential diagnosis of central nervous system disease is emphasized.

Acknowledgment is made to Dr. Joe M. Strayhorn for permission to report this case and to Dr. William F. Meacham for suggestions and comments which have been valuable in preparing this paper.

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OBSTRUCTION TO LEFT ATRIAL OUTFLOW BY A SUPRAVALVULAR STENOSING RING

NORMAN J. JOHNSON, M.D.,* AND KATHARINE DODD, M.D.
LITTLE ROCK, ARK.

THE occurrence of a supravalvular stenosing ring of the left atrium has been recently reported by Rogers and associates.[1] Two similar formations have been observed, one mentioned but not fully reported by Edwards,[1] and the other described with minimal detail by Kipkie and Johnson.[2] It seems of interest to record a fourth case in which such a ring was very highly developed and might have been amenable to surgical correction had its presence been suspected during life. The lesion in the present instance, unlike those previously reported, was complicated by the presence of a patent ductus arteriosus.

CASE REPORT

The patient, an 11-year-old girl at the time of her fatal illness in 1953, was born by cesarean section Sept. 3, 1941. She weighed 6 pounds 4½ ounces at birth. Her two older siblings, both boys, were apparently normal. In the first year of life she is said to have had considerable difficulty in breathing, and oxygen was administered on many occasions. She also had frequent episodes of vomiting.

A physical examination in February, 1942, revealed a poorly developed, pallid child. There was vigorous pulsation of the peripheral arteries. A short, moderately loud systolic murmur was audible all over the precordium. Slight cardiac enlargement to the left was reported on the roentgenogram of the chest. The examiner expressed his opinion that the child "apparently had a rather large *patent ductus arteriosus.*"

Motor and mental development proceeded at a normal rate, but growth was slow. The child weighed 11 pounds 10 ounces at age 11 months, and 16 pounds at age 2 years. By October, 1945, at the age of 4 years, she was doing unusually well and had no symptoms referable to her heart. Her play was active without undue fatigue. She had achieved a height of 37½ inches and a weight of 28¾ pounds. A loud systolic murmur at the left sternal border near the base of the heart was the only notable physical finding. Large P waves and right ventricular preponderance characterized the electrocardiogram. During 1947 the patient seemed well except for two episodes of pneumonia which required hospitalization.

The child was examined in 1949 independently by two pediatric cardiologists. Their findings were strikingly similar. There was a prominent systolic murmur over the base of the heart. Rough presystolic and systolic murmurs were heard at the mitral area. A mid-diastolic murmur was also present at the apex. The pulmonic second sound was accentuated. There was a thrill at the apex, believed to be in presystole by one observer and in systole by the other. The patient's blood pressure was 120/50. A faint capillary pulse was present. These two latter findings are suggestive of the presence of a patent ductus

From the Department of Pediatrics, University of Arkansas Medical Center.

*Present address: Memorial Medical Center, Williamson, W. Va.

arteriosus. The examiners were also impressed with the findings in the mitral area and were convinced of the presence of mitral stenosis, and possibly of mitral insufficiency also. The association of interatrial septal defect with mitral stenosis, which was previously commonly accepted, colored their interpretation in favor of a Lutembacher's syndrome. Prominence of the pulmonary artery sector, increase in the vascularity of the lung fields, and enlargement of both auricles and of the right ventricle were observed fluoroscopically.

From 1949 on, the patient was under the care of her local pediatrician. Her general health seemed to be good until, shortly after an episode diagnosed clinically as streptococcal pharyngitis, she developed dyspnea and anasarca, for which she was hospitalized Feb. 18, 1953, at St. Vincent's Infirmary, Little Rock. Acute glomerulonephritis was suspected. In the hospital the child remained very dyspneic despite continuous administration of oxygen in a tent. The liver was enlarged and tender. The anasarca failed to respond to administration of digitalis, ammonium chloride, and Mercuhydrin. Fever was present throughout her hospital stay. When we saw her she was in the terminal phase of her illness. Her constant discomfort, incessant complaints, lack of cooperation, and the multiplicity of physical findings rendered an adequate cardiac appraisal impossible. Prior to her death numerous skin hemorrhages appeared over her body.

Leukocytosis of 12,000 to 28,000, with a predominance of polymorphonuclear cells, was constant. The serum nonprotein nitrogen on March 11, 1953, was 85 mg. per cent, and two days later was 80 mg. per cent. Serum electrolyte studies on both occasions were compatible with a mild hypochloremic alkalosis. Repeated urinalyses revealed 1 to 4 plus albuminuria, many red blood cells, and casts. A roentgenogram of the chest revealed marked cardiac enlargement, increased pulmonary vasculature, a prominent pulmonary artery sector, pulmonary edema, and possible pneumonia.

The patient remained in cardiac failure until she died on March 22, 1953.

Pathologic Findings.—The significant necropsy findings were demonstrated primarily in the heart, lungs, and kidneys, and in the small arteries of other organs as well. The right ventricular wall measured 12 mm. in thickness; the left, 18 to 20 mm. The ductus arteriosus was patent and its lumen was 8 mm. in diameter. About 4 mm. above the mitral valve a fibrous ring completely encircled the left atrium. This well-organized structure protruded far into the atrial cavity, leaving an orifice only 1 cm. in diameter. There was some shortening of the chordae tendineae with slight rolling of the mitral valve edges. The papillary muscles were hypertrophied.

The lungs were grossly edematous. Many petechiae and small infarcts were present. There was marked hilar lymphadenopathy, the nodes measuring 3 by 4 cm. The kidneys appeared pale and swollen.

Microscopic examination revealed thickening of the mitral valve leaflets and the valve ring by dense collagen tissue showing large zones of basophilic degeneration. In the region of the mitral ring there was encroachment of the scar tissue on the myocardium, areas of viable myofibrils alternating with areas of fresh scarring. The thickened endocardium extended from the base of the valve along the atrial wall for about 4 mm. where there was a valvelike protrusion comprised of connective tissue with considerable numbers of elastic fibers. Above this point the atrial endocardium was thin. Immediately adjacent to the valve the ventricular endocardium was markedly thickened with large amounts of elastic tissue. The myocardium of the ventricle showed moderate hypertrophy of the muscle fibers.

Hemorrhagic infarcts and congestion were prominent in the lung sections. Severe intimal thickening was

present in the small arteries. Collagen tissue was greatly increased in amount in the medial coat of the small arteries, and some inflammatory cells were seen. In some areas, the arterial lumina were so small as to be virtually obliterated; in other areas, definite organizing thrombi plugged the small arteries.

The kidney glomeruli were large and cellular. There was an increase in collagen tissue within the capillary tuft. Tubular damage was extensive, the tubules varying markedly in size and shape. Cloudy swelling was present in some tubular cells; in others, there was a loss of nuclear pattern. Many of the tubules contained casts, some containing red cells, others consisting only of dense, homogeneous debris.

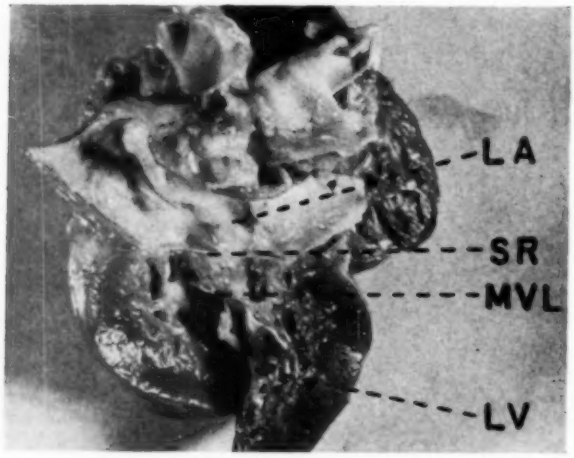

Fig. 1.—Photograph of open heart. *LA*, Left atrium; *SR*, stenosing ring; *MVL*, mitral valve leaflet; *LV*, left ventricle.

Changes similar to those seen in the small arteries of the lung were found in small arteries in the liver, spleen, adrenals, and pancreas. There were a great increase of collagen tissue and marked compromise of the vessel lumina.

DISCUSSION

The origin of the supravalvular stenosing ring of the left atrium is not immediately apparent. Edwards'[1] patient with corrected transposition of the great vessels had insufficiency of the left atrioventricular valve. The report of Kipkie and Johnson[2] does not contain any reference to mitral insufficiency. Rogers and co-workers[1] advanced an ingenious theory to explain the development of the lesion in their case. Endocardial sclerosis in the left ventricle was believed to have shortened the chordae tendineae, thereby producing insufficiency of the mitral valve. The regurgitant jet of blood through the insufficient mitral valve orifice produced a localized "jet lesion" in the atrium. The cusplike projection of the atrial endocardium thereupon redirected the jet, so that another "jet lesion" was formed in contiguity to the first. The process continued until a complete stenosing ring was eventually formed. In our patient there was evidence on clinical grounds for the existence of mitral insufficiency. At necropsy, the chordae

tendineae were shortened, and there was rolling of the mitral valve edges. It seems conceivable that her supravalvular left atrial stenosing ring may have developed in the manner described by Rogers and associates.[1] It seems equally possible that the stenosing ring may have been a congenital lesion of the auricular endocardium.

The clinical course of our patient's terminal illness suggests the possibility of periarteritis nodosa, rheumatic fever, or other collagen disease. Certain changes in the walls of small arteries are also suggestive, although not absolutely diagnostic, of collagen disease. The pulmonary congestion; the chronic passive congestion of liver, spleen, and kidneys; alteration in the pulmonary vessels; and the left atrial enlargement and right ventricular hypertrophy could well stem from the obstruction to the outflow of blood from the left atrium by the stenosing ring. The marked hypertrophy of the left ventricle may be attributed to the presence of a left-to-right shunt of some magnitude through the ductus arteriosus or to mitral insufficiency or both. Pulmonary hypertension must have been present, but did not produce a significant reversal of flow through the ductus, as the child remained acyanotic. Shunting of blood from the aorta into the pulmonary circulation may have aggravated the pulmonary vascular changes.

Surgical obliteration of a patent ductus arteriosus is now a common procedure. Operative relief of mitral valvular stenosis has been successfully accomplished in adults, in children, and even in infants.[3, 4] The production of mitral insufficiency may nullify the benefit obtained from such surgery. In our patient, surgical correction of the patent ductus arteriosus and of the supravalvular stenosing ring of the left atrium might have benefited the circulation greatly.

SUMMARY

The case of a girl who died at 11 years of age, of heart failure, and who was found at post-mortem examination to have a patent ductus arteriosus and a supravalvular left atrial stenosing ring is reported. If the stenosing ring was a congenital malformation its recognition by modern methods of investigation might have permitted surgical relief.

This case is reported through the courtesy of Dr. Sam Phillips.

The post-mortem examination was performed at St. Vincent's Infirmary by Dr. William S. Orr.

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CONSIDERATIONS ON AN UNRECOGNIZED MEDIASTINAL CYST

JOHN STORER, M.D., AND CHAHNOUR KIRAGUS, M.D.
CLEVELAND, OHIO

THERE have been numerous reports dealing with the classification, recognition, and treatment of mediastinal cysts. With few exceptions the authors have included only radiologically detectable lesions in their theses.

This report is concerned with the importance of the diagnostic consideration of a mediastinal cyst presenting obstructive respiratory symptoms in the face of a normal radiologic picture.

CASE REPORT

R. S., a 9-month-old white male child, was admitted to Huron Road Hospital on April 29, 1956, because of respiratory distress. A review of the past history revealed that he had developed obvious difficulty in breathing a few months after birth. This slowly progressed in severity and became associated with a hacking cough, poor feeding habits, and a hoarse cry. Just prior to admission, his respirations became more labored and he developed cyanosis. Physical findings of note were confined to the chest. There were moist râles and rhonchi scattered throughout. The breath sounds were diminished over the upper third of the right chest anteriorly.

Laboratory data at this time were as follows: urinalysis—specific gravity 1.010, acetone +, albumin ++, sugar negative, red blood count negative, white blood count negative, hemoglobin 11.7 grams, hematocrit 34; white blood count 10,750—polymorphonuclears 42, eosinophils 2, lymphocytes 56, stool ++++ for tryptic activity in 1:100 dilution. Throat smear was positive for Aerobacter. An x-ray of the chest revealed atelectasis of the right upper lobe (Fig. 1).

Bronchoscopy disclosed the presence of diffuse tracheobronchitis and gave no hint of the obstructive factor in the right upper lobe. The patient was treated with antibiotics, high humidity, and general supportive measures. Four days later there was some clearing of the right upper lobe, but the left upper lobe had become atelectatic. The same therapeutic regimen was continued, however, and gradual improvement was noted over a period of several weeks. After discharge from the hospital, he continued to exhibit periodic dyspnea and cough but was much improved over his former status.

On May 9, 1956, he developed marked difficulty in breathing, restlessness, and periodic stupor. He was readmitted on May 11, 1956, in acute distress. Pallor was pronounced and cyanosis was noted in the mucous membranes. The temperature was 38.5° C. Respirations were 54 per minute. A chest x-ray showed atelectases of the right upper lobe. The child died shortly after admission, before therapy could be instituted.

Post-mortem examination was performed within one hour of death. The pertinent findings were confined to the thoracic structures. Upon entering the chest a cystic lesion was noted in the superior mediastinum between the aorta and the superior vena cava. These structures were slightly displaced laterally by this cyst. The bulk of the cystic lesion lay behind the

From the Department of Thoracic Surgery, Huron Road Hospital.

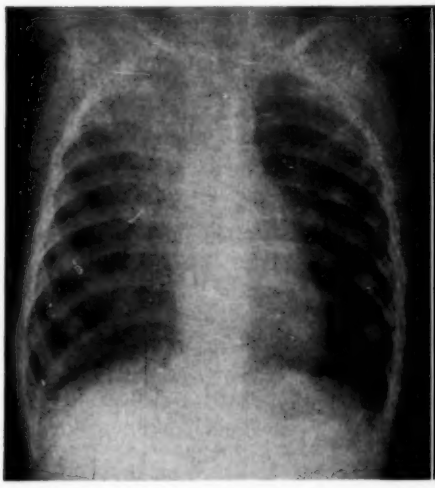

Fig. 1.

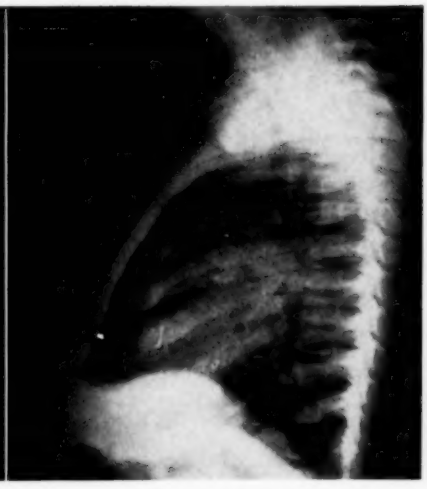

Fig. 2.

Fig. 1.—Posteroanterior film of the chest.
Fig. 2.—Lateral film of the chest.

Fig. 3.

Fig. 4.

Fig. 3.—Findings on opening the chest. The cyst is at the arrow point, between the aorta and the superior vena cava.

Fig. 4.—The appearance of the cyst after it had been partially dissected and displaced posterolaterally.

heart. It markedly compressed the right superior pulmonary vein. The dissection of the cyst showed it to be an ovoid structure 4.5 by 3 cm., attached to the trachea at the bifurcation. By direct pressure it had completely obstructed the right upper lobe bronchus. Examination of the lungs revealed complete consolidation of the right upper lobe. The remainder of the lung was normal. Microscopic examination of the lung confirmed the impression of interstitial pneumonia and atelectasis. Sections from the wall of the cyst revealed the lining epithelium to be respiratory in type. Other components of the respiratory system, such as cartilage and mucous glands, were present. It was concluded that the death of the infant was caused by interference with respiration and obstruction to the flow of blood to the left heart.

The indelible clarity with which the autopsy findings relate to the clinical symptomatology suggest that one consider several factors. Primarily, a mediastinal cyst may be so located and of such a density that it is neither radiologically detectable nor does it displace other visible structures sufficiently so that the diagnosis may be confirmed. Secondarily, the presence of a mediastinal mass should be suspected in all patients presenting evidence of respiratory tract obstruction when the diagnosis is not otherwise confirmed.

It is questionable if any diagnostic adjuvant would have been of help in this instance. Bronchoscopy certainly did not suggest the cause and it is not likely that an esophagram would have clarified this picture. It is doubtful if the forward displacement of the pulmonary veins would have been visualized by angiocardiography and thereby increased one's suspicion concerning the possibility of such a lesion. Possibly, the separation of the superior vena cava and aorta would have been seen. The inevitable fact remains, however, that exploratory thoracotomy would have been the only method whereby the true nature of the illness would have been disclosed and thereby adequately treated.

The most important factors in effecting a favorable outcome in such a problem are an awareness of the possibility of such a phenomenon, a high index of suspicion and the fortitude to proceed with exploratory thoracotomy.

SUMMARY

1. A case of a radiologically nondetectable mediastinal cyst is presented.

2. The importance of considering exploratory thoracotomy in undiagnosed respiratory tract obstructions is stressed.

FOREIGN BODY (PAPER CLIP) IN THE ESOPHAGUS OF A YOUNG INFANT

SAMUEL J. NICHAMIN, M.D., AND WILLIAM S. GONNE, M.D.
DETROIT, MICH.

THE accidental swallowing of foreign objects by older infants or young children cannot be regarded as an unusual or rare occurrence in the practice of any physician dealing with this age group. The instinctive developmental hand-to-mouth attribute of these growing individuals, coupled with their intense curiosity about an expanding world, provides an unending catalogue of diverse and miscellaneous foreign objects, inhaled or ingested. Their active participation in such accidental swallowing is a well-warranted presumption, unless otherwise contradicted by a reliable history.

Small consideration has hitherto been given to the problem of opaque foreign bodies found lodged in the esophagus of infants under 6 months of age, who are still developmentally unable to grasp objects for insertion into the mouth. Here the infant's role is entirely a passive one. The presence of a foreign body thus located in a roentgenogram is mute evidence of someone's carelessness or guilt. Aside from the medical importance, such foreign bodies present medicolegal implications for anyone entrusted with the immediate care of young infants.

From the Department of Pediatrics and the Department of Otolaryngology, Wayne University College of Medicine, and the Children's Hospital of Michigan.

In this young age group, as well as for the older infant and child, a reliable history is usually not available. In effect, the correct diagnosis is often obscured by the predominance of respiratory symptoms and signs that may simulate pulmonary diseases. Such factors were pertinent in the case we are herewith reporting.

CASE REPORT

After having been under the care of the family physician since birth, this patient was first seen at the age of 3¾ months with a history of unremitting attacks of respiratory difficulty. The mother had been aware of raspy, rapid breathing that had begun sometime during the neonatal period. At 3 weeks of age fairly severe coughing associated with high fever and dyspnea was noted, for which bronchitis was diagnosed and treated with penicillin and Aureomycin. There was fluctuation in the severity of these attacks, which occurred intermittently over a period of several months. Despite the administration of various antibiotics no definitive improvement in the respiratory symptoms or signs had occurred. Feedings were always taken well, and gain in weight was apparently normal. After the first month the parents became aware of a "rattling" type of breathing, which became progressively more marked. The temperature remained within normal limits, even during severe attacks of

cough and dyspnea. A roentgenogram of the chest revealed the presence of a foreign body in the upper portion of the esophagus. The infant was admitted to the hospital under our care at the age of 4 months.

Birth weight was 8 pounds 8 ounces. This was the mother's third pregnancy. There was a normal spontaneous delivery with vertex presentation. The infant breathed and cried spontaneously. Feedings were taken well. Jaundice became apparent at the age of 2 to 3 days. No cyanosis or dyspnea had been present during the first days of life.

Fig. 1.—Anteroposterior chest x-ray, showing a circular, wire paper clip in the upper third of the esophagus.

There were no relevant facts pertaining to the prenatal or family history.

On admission to the hospital the infant appeared to be in fairly good condition except for evidence of stertorous respirations. The temperature was 99.6° F. rectally. Coarse breath sounds and rhonchi were heard diffusely throughout both lung fields. Slight bilateral retraction of lower chest walls was observed. The weight was 14 pounds 1 ounce. Eye, ear, nose, and throat findings were negative. The heart and abdomen revealed normal findings. Skin and tissue turgor was of good quality. Urinalysis was negative; hemoglobin, 11 grams; white blood count, 15,800; polymorphonuclear cells, 35; lymphocytes, 60; monocytes, 2; and eosinophils, 3. Platelets were adequate. There were 4 bands. The Mazzini test was negative and the Mantoux (1:1,000) was negative. The throat culture showed a heavy growth of *Streptococcus viridans,* a moderate growth of *Escherichia coli* and *Streptococcus hemolyticus,* and *Neisseria*

Fig. 2.—Lateral chest x-ray, with the foreign body (paper clip) lying in the coronal plane of the cervical segment of the esophagus, above the sternoclavicular joint.

catarrhalis. Test of the stools for blood was negative.

On the day following admission esophagoscopy was performed by one of us (W. S. G.). No foreign body was present in the larynx. A metallic foreign body was visualized in the esophagus. After an unsuccessful attempt at removal it was finally dislodged and followed down to the cardia of the stomach. Fluoroscopic study soon thereafter showed a circular, wirelike, metallic foreign body about 1.6 cm. in diameter lying in the

stomach. After an uneventful passage through the remainder of the gastrointestinal tract, a round, metallic, and corroded paper clip was retrieved from a stool specimen, forty-eight hours after esophagoscopy.

Because of the intensely inflamed condition of the esophageal mucous membranes, food was withheld for twelve hours following the instrumentation. During the next two days fluoroscopic examination revealed progressive passage of the foreign body through the alimentary canal, and finally in the rectum. No clinical complications were evident. Fluoroscopic and roentgen-ray examination of the esophagus forty-eight hours after instrumentation showed a free passage of the barium through the esophagus, with no sign of obstruction or of any intrinsic lesion at any level; and the esophagus appeared normal in contour and position. It was noted, however, that the trachea had a persistently narrow anteroposterior diameter, particularly about its cervicothoracic junction. There was no indication of an abnormal cervical or mediastinal mass. No abnormalities of the heart, lungs, or mediastinum were apparent.

Fig. 3.—Anteroposterior x-ray of abdomen after esophagoscopy, showing the foreign body lying in the stomach.

Complete subsidence of both respiratory symptoms, as well as objective chest findings, occurred almost simultaneously with the removal of the foreign body from the esophagus. Subsequent to this procedure there has been complete absence of any respiratory difficulty. The infant's growth and development have progressed normally. At 20 months of age the patient's height was 32 inches and his weight, 25 pounds.

Fig. 4.—X-ray examination of the esophagus forty-eight hours after esophagoscopy, and after free passage of barium, revealing no abnormalities in contour or position.

COMMENT

The possibility of foreign body inhalation or ingestion is an ever-present consideration in otherwise unexplained pulmonary symptoms or signs that are refractory to adequate administration of various types of antibiotic therapy. The absence of a reliable history from parents or attendants should have no bearing on the necessity for a roentgenogram of the chest in such instances.

There is need for active intervention without undue delay in the removal of any type of foreign body arrested in the esophagus. Because of its inherent anatomic and physiologic characteristics, the esophagus is often incapable of propelling even relatively small, smooth foreign objects. An expectant or laissez-faire attitude cannot be condoned in the presence of any solid foreign body lodged in the esophagus, no matter what its size or configuration. The foreign object in our case, a small, round paper clip, with no sharp protruding points, might be viewed as relatively innocuous; but with time and extended contact, pressure necrosis and perforation of the esophageal wall might have developed.

The most common locale for lodgment of a foreign body in the esophagus is in its upper cervical segment, as in our case. This has been attributed to a physiologic narrowing at this level, produced by muscular contraction and adjoining viscera in addition to a relatively weak esophageal musculature.

Many campaigns have been, and are being, promoted for the prevention of accidents in the runabout or preschool child. The indoctrination of parents should also encompass prophylaxis of accidents in the defenseless young infant, relating to the potential inhalation or ingestion of any small foreign objects in the baby's immediate vicinity. Furthermore, nurses or attendants should be cautioned about eliminating any pins, needles, safety pins, buttons, or loose jewelry on their garments before handling babies. These various small objects can easily slip out and drop into a baby's mouth during routine infant care or feeding. In our case, the possible occurrence of such an accident could not be eliminated. Awareness of the potential mayhem that can be inflicted upon a small infant by an older sibling is another factor in the prophylaxis of foreign body ingestion in the age group under 6 months.

Since the mouth of infants and children can be regarded as an exploratory organ, it serves as the portal of entry for foreign bodies reaching the airway as well as the esophagus. If not swallowed via the latter route, they may be inspired during the inspiratory phase of coughing, and lodge in the larynx or lower down in the respiratory tract. Paroxysms of coughing, gagging, and dyspnea serve as explicit evidence of foreign body inhalation, whereas such symptoms may be lacking or only transient during ingestion of a foreign body that becomes lodged in the esophagus. Dysphagia may be an important symptom soon after the foreign body becomes caught in the cervical segment of the esophagus; but, in a small infant, as in the above-mentioned case, this symptom cannot be definitely ascertained.

With foreign body obstruction of the esophagus the concurrent presence of symptoms of bronchial involvement has been a familiar clinical observation. The clearing and disappearance of the chest findings subsequent to the removal of such a foreign object affords a syndrome with a strikingly happy ending. One can infer that anything lodging or caught in the wall of the esophagus would have an adverse effect on its motility. The resultant "overspilling" of esophageal secretions would

lead to their aspiration into the tracheobrnochial tree. The presence of this extraneous material in the bronchi provides the etiologic factor for the occurrence of bronchitis in these cases. Irreversible or residual pathology of the air passages is probably not involved, provided removal of the foreign body in the esophagus is not unduly delayed. The case herewith reported well exemplifies the favorable sequence of clinical events upon such removal.

SUMMARY

Attention has been directed to the need for constant vigilance in safeguarding young infants from accidentally ingesting small foreign objects that may become lodged in the esophagus. Prompt dislodgment and removal of these objects may avoid dire complications. If undiagnosed, their lodgment in the esophagus may give rise to respiratory symptoms and findings of a bronchitis unresponsive to any medication. This pulmonary involvement is dissipated after removal of the foreign body.

The essentiality of roentgen-ray examination of the chest even in young infants with unexplained respiratory symptoms cannot be under estimated in the early detection of a foreign body arrested in the esophagus.

In our case it was conjectured that the accidental ingestion of the foreign body (paper clip) that became lodged in the esophagus might have occurred during the neonatal period, whence the respiratory symptoms had their onset.

We hear from Danbury, that last week the wife of Benjamin Starr of that place, was safely delivered of three male children, one on a Thursday, and two on the Saturday following; The first died a few hours after its birth, the other two appear likely to live. She has had two children at a birth once before: is now in the 29th year of her age, the mother of nine living children, the eldest little more than 10 years of age; is herself a twin, one of fifteen children, born of the same mother, who died before she was forty years of age.

NEW LONDON GAZETTE, September 23, 1774.

THE EARLY DEFINITIVE DIAGNOSIS OF PATIENTS WITH CONGENITAL HEART DISEASE

FORREST H. ADAMS, M.D.
LOS ANGELES, CALIF.

PREVIOUS articles have attempted to emphasize the need and importance of early definitive diagnosis in patients with atypical patent ductus arteriosus.[1, 2] The purpose of this communication is to extend this line of reasoning to include *all patients* with congenital heart disease. Such a consideration is based on the following five points:

1. The high morbidity and mortality rates for such patients during the infancy period.
2. The early age at which certain operable lesions reach the stage of inoperability by present methods.
3. The apparent increased tolerance of the young patient's heart for corrective or palliative surgery.
4. The psychological advantages in early amelioration of cardiovascular signs and symptoms.
5. The greater potential for return of the cardiac status toward the normal with early surgery.

THE HIGH MORBIDITY AND MORTALITY OF PATIENTS WITH CONGENITAL HEART DISEASE

It is known from at least two sources[3, 4] that 60 to 80 per cent of patients dying with congenital heart disease do so during the first two years of life. It is my feeling that a significant number of these patients have heart lesions potentially operable by present methods. In support of this point of view, Tables I, II, and III adapted from Boesen and Vendel,[5] are presented, which are an analysis of the post-mortem data obtained from 1,145 children dying of congenital heart disease under 4 years of age in Scandinavia. The original material has been rearranged into three groups: operable lesions; surgery possible (procedure still in developmental stage); no surgery at present. Of these 1,145 cases, 356 (Table I), or one-third consist of lesions for which corrective or palliative surgery is of *proved value*. Five hundred sixty-three (Table II), or one-half, had lesions for which surgery is now being attempted and in many instances is either of curative or of palliative value. Only one-fifth of the patients (Table III) died of lesions for which there is no surgical procedure at the present time.

Congenital heart lesions are not only a significant cause of death in infancy but are also a significant cause of morbidity. Keith[6] has recently reviewed his experience in the diagnosis and treatment of *heart failure* in the pediatric age group. Three hundred four patients with heart failure were seen, of whom 90 per cent were under 1 year of age. Fig. 1 shows the cause of heart failure for those patients under 1 year of age. In addition to the high

From the Department of Pediatrics, School of Medicine, University of California at Los Angeles.

incidence of transposition of the great vessels and coaretation of the aorta as a cause of heart failure, of particular interest is the high incidence of endocardial fibroelastosis, particularly after the first month of life. Studies are currently in progress in our laboratories to enable better understanding of the physiologic disturbances produced in this condition.

THE EARLY AGE AT WHICH CERTAIN OPERABLE LESIONS REACH THE STAGE OF INOPERABILITY BY PRESENT METHODS

It is becoming increasingly evident that in the instance of at least two congenital heart lesions, patent ductus arteriosus and interventricular septal defect, there is a far-advanced clinical situation in which surgery by present methods is probably contraindicated.

TABLE I. CAUSE OF DEATH UNDER 4 YEARS OF AGE (1,145 CASES)*
OPERABLE LESIONS

DIAGNOSIS	TOTAL	DIED LESS THAN			
		30 DA.	150 DA.	1 YR.	>1< 4 YR.
Coarctation of aorta	83	40	70	80	3
Patent Ductus arteriosus	70	24	54	65	5
Tetralogy of Fallot	48	15	24	36	12
Atrial defect (secundum)	35	10	26	31	4
Atrial defect (primum)	13	1	7	11	2
Aortic stenosis, valvular	30	14	25	29	1
Tricuspid stenosis	30	11	21	28	2
Atrial defect + PDA	28	19	26	27	1
Pulmonary stenosis	19	9	11	16	3
Total	356	143	264	323	33

*Adapted from Boesen and Vendel: VIII International Pediatric Congress.

TABLE II. CAUSE OF DEATH UNDER 4 YEARS OF AGE (1,145 CASES)*
SURGERY POSSIBLE

DIAGNOSIS	TOTAL	DIED LESS THAN			
		30 DA.	150 DA.	1 YR.	>1< 4 YR.
Ventricular defect	148	51	107	142	6
Ventricular defect + PDA	65	34	54	63	2
Ventricular defect + ASD	15	1	10	14	1
Ventricular defect + PDA + ASD	12	5	10	12	
Pulmonary stenosis + ASD/-USD/PDA	33	13	24	29	4
Atrioventricular communis	33	6	22	33	
Complete transposition	167	78	138	163	4
Single ventricle	90	52	80	88	2
Total	563	240	445	544	19

*Adapted from Boesen and Vendel: VIII International Pediatric Congress.

TABLE III. CAUSE OF DEATH UNDER 4 YEARS OF AGE (1,145 CASES)*
NO SURGERY AT PRESENT

DIAGNOSIS	TOTAL	DIED LESS THAN			
		30 DA.	150 DA.	1 YR.	>1< 4 YR.
Hypoplasia of left ventricle	63	43	60	63	
Truncus communis	48	33	42	47	1
Hypoplasia of aorta	42	21	36	39	3
Diverse	73	22	47	68	5
Total	226	119	185	217	9

*Adapted from Boesen and Vendel: VIII International Pediatric Congress.

In the severe form of "reverse" patent ductus arteriosus, where the major portion of the flow through the ductus arteriosus is from pulmonary artery to aorta, the operative mortality is approximately 100 per cent, for reasons not well understood.[7] In contrast to this, in patients where the major portion or all of the flow through the ductus arteriosus is from aorta to pulmonary artery, the operative mortality is below 1 per cent.[8] A ventricular septal defect is a systolic pressure in the right ventricle which exceeds that in the left ventricle, so that a right-to-left interventricular shunt occurs.[10] Most of these patients with nearly balanced pressures in the right and left ventricles have extensive changes in the intima and media of the pulmonary arterial tree.[10] Recent evidence has been presented to show that the operative mortality in this group of patients also approximates 100 per

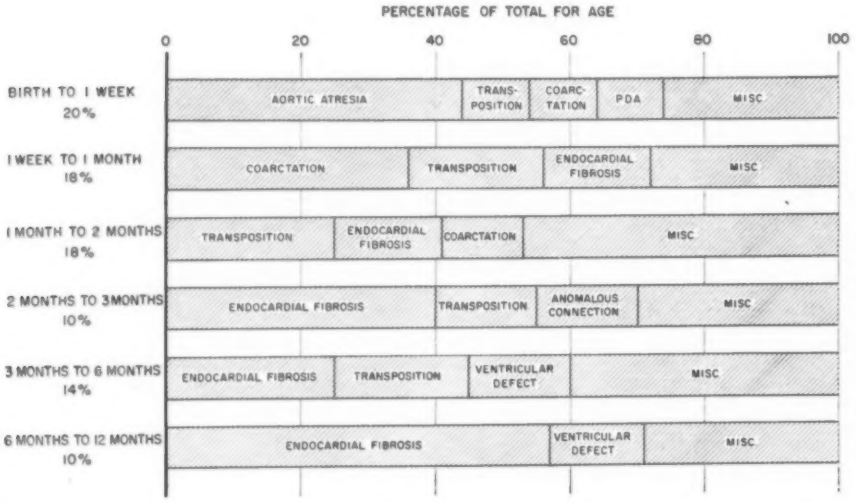

Fig. 1.—Cause of heart failure according to age (304 cases). (Adapted from Keith: Pediatrics **18**: 491, 1956.)

recent paper has presented evidence to suggest that patients with a partial "reverse" ductus arteriosus operated upon at an early age can survive such surgery even though there is some reverse flow.[9] The main problem is early recognition and definitive treatment.

Eisenmenger complex has long been recognized as a form of interventricular septal defect. The main aberration that distinguishes it from simple interstitial, in sharp contrast to the much lower mortality for patients without such elevated right ventricular pressures.[11] Clear-cut evidence is not available to show that right ventricular and pulmonary hypertensions progress with time. However, severe forms of the disease with pulmonary hypertension are known to exist in the infancy and early childhood period. It is entirely possible that the pathological changes present in the lungs

of younger patients with the disease will not be so extensive or irreversible at this earlier age.

THE APPARENT INCREASED TOLERANCE OF THE YOUNG PATIENT'S HEART TO CORRECTIVE OR PALLIATIVE SURGERY

As yet, there has been no clear-cut evidence presented to indicate the optimal age for cardiac surgery for the various types of malformations. In some centers, it has been the practice to postpone such surgery where possible until late in childhood. In other centers, the trend has been to operate for certain of the malformations at earlier ages; in some instances this has amounted to performing surgery as soon as the diagnosis is clearly established.

It is my impression that, when the various factors are taken into consideration, the heart of the younger child or infant tolerates cardiac surgery better than the older one's. This statement is based on the incidence of cardiac irregularities, disturbances in pressure relationships, complications due to friability of vessels and bleeding tendencies, incidence of postoperative heart failure and electrolyte disturbances.

The problems relating to size of the vessels, problems relating to fluid administration (particularly with the extracorporeal pump), and the difficulty of recognizing subjective symptoms in a noncommunicative patient must be acknowledged as deterrents to early surgery.

THE PSYCHOLOGICAL ADVANTAGES IN EARLY AMELIORATION OF CARDIOVASCULAR SIGNS AND SYMPTOMS

Physicians who deal exclusively or extensively with children are well aware of the importance of early childhood events, in personality development. Knowledge of the presence of a congenital heart lesion has its effect on the child, parents, and society (friends, school, etc.). Great concern on the part of the physician and parents over the somatic aspects of a child's life can affect the child. This effect must in some way be related to the nature and duration of the concern.

Where possible, every attempt should be made to keep the manifest concern to a minimum not only through the nature of each examination and visit to the doctor, but also by the early performance of corrective or palliative surgery. In this connection any surgical procedure prior to 2 years of age is generally free of psychiatric repercussions. As the child becomes older, the effect of such surgery approximates that produced in an adult. If early corrective surgery is performed, the child can then be treated normally by society even though occasional examinations by the physician may be necessary.

THE GREATER POTENTIAL FOR RETURN OF THE CARDIAC STATUS TOWARD NORMAL WITH EARLY SURGERY

Evidence is also meager or lacking regarding the return of the cardiovascular system toward normal following cardiac surgery. However, it seems reasonable to expect that the younger patient, who still has considerable growth potential in most of his tissues, will have the greatest return toward normal. Such return toward normal should be expected in the hypertrophied hearts, in the dilated hearts, in the systemic pressures (coarctation of the aorta), and in the

pulmonary artery pressures (lesions associated with changes in the pulmonary arterioles).

SUMMARY

Five reasons have been presented to support the concept of early definitive diagnosis of patients with congenital heart disease:

1. The high morbidity and mortality rates for such patients during the infancy period.

2. The early age at which certain operable lesions reach the stage of inoperability by present methods.

3. The apparent increased tolerance of the young patient's heart for corrective or palliative surgery.

4. The psychological advantages in early amelioration of cardiovascular signs and symptoms.

5. The greater potential for return of the cardiac status toward the normal with early surgery.

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THE TRANSPLACENTAL TRANSMISSION OF POLIOMYELITIS

PERCY BARSKY, M.D.,* WINNIPEG, CANADA, AND A. J. BEALE, M.D. (LOND.), DIP. BACT. (LOND.), TORONTO, CANADA

WELL-DOCUMENTED evidence supports the conclusion that the viruses of rubeola, varicella, vaccinia, lymphocytic choriomeningitis, and encephalitis may all pass the placental barrier.[1-5] The occurrence of intrauterine poliomyelitis, on the other hand, has been the subject of considerable controversy. While the incidence of poliomyelitis in pregnant women has increased,[6] no evidence of the disease in the fetus had been detected until 1954, when the first known recorded case of intrauterine poliomyelitis infection was described, by Schaeffer and associates.[7] It was also in that year that Swarts and Kercher[8] recorded a case of poliomyelitis in a newborn infant, in which intrauterine infection was plausible.

The present paper deals with a series of six infants born to mothers suffering from the acute phase of poliomyelitis. They were admitted to the Winnipeg Municipal Hospitals during the five-month period from July to November, 1953. A total of 2,284 cases of poliomyelitis occurred during this period, and 1,158 patients came to this hospital for treatment. Fifty-one patients with poliomyelitis occurring during pregnancy were admitted on this service, and these cases have been the subject of a previous report.[9] Meconium and cord blood from six babies born to these mothers were examined for poliomyelitis virus. These six cases, which are the basis of this study, are presented as evidence that the transplacental transmission of poliomyelitis virus can occur.

This work was done on the Acute Poliomyelitis Service of the Winnipeg Municipal Hospitals during 1953. The virus studies were carried out at the Research Institute, Hospital for Sick Children, Toronto.

*Address: 1471 Main St.

METHODS

Virus Studies.—

Specimens: Meconium diluted approximately 1:20 in medium 199,[10] containing 500 units of penicillin and 250 meg. of streptomycin per milliliter was shaken thoroughly with glass beads at room temperature for twenty minutes. The cord blood sample was added to culture directly.

Trypsinized monkey kidney cultures were prepared by a modification of the method of Youngner.[11] Medium 199 with 2 per cent horse serum was used to grow the cells, and before inoculation the cultures were changed into fresh medium 199 without horse serum. Virus isolation tests were performed by adding 0.1 ml. of the specimen to three culture tubes and observing them under the low power of the microscope daily for cytopathogenic changes. Negative cultures were observed for seven days and then subcultured into three more tubes which were again observed for seven days. If these cultures remained healthy a negative result was recorded.

Typing of cytopathogenic agents: If a cytopathogenic effect was observed, the tissue culture fluid was removed and mixed with an equal volume of hyperimmune monkey serum (Brunhilde type 1, Lansing 2, and Leon type 3). After one hour at room temperature, two cultures were inoculated with 0.1 ml. of each mixture. The results were read after seven days.

CASE REPORTS AND RESULTS OF VIRUS STUDIES

CASE 1.—On Aug. 12, 1953, a 24-year-old mother, who was almost at full term, was admitted to the Municipal Hospitals. On admission she complained of mild pain in the lower limbs, weakness, headache, and stiff neck of three days' duration. Lumbar puncture showed an elevated cell count with a predominance of polymorphonuclears, a normal pressure, and a normal protein content. Two days later she developed hyperpyrexia, severe pain in neck and shoulder muscles, and flaccid paralysis of both legs. On August 26, fetal heart sounds were absent and fetal movements ceased. The next day she was delivered of a male stillborn infant, via low forceps. The mother survived, with residual flaccid paralysis of both lower limbs and weakness of her abdominal muscles.

Autopsy summary on the stillborn male fetus: There was aspiration of amniotic fluid and numerous horn lamellae were present in the alveolae. There were multiple subpleural and subepicardial hemorrhages. There was no gross or microscopic evidence of poliomyelitis.

Type 1 poliomyelitis virus was isolated from the meconium. No virus was isolated from the cord blood.

CASE 2.—A 22-year-old, eight months pregnant woman was admitted on Sept. 5, 1953. She was acutely ill, with paralysis of both legs and a history of abdominal pain and weakness for ten days. Lumbar puncture showed a clear fluid with 130 white blood cells per cubic centimeter and a normal pressure. Paralysis spread rapidly to involve the intercostal muscles and palate. Tracheotomy was performed because of pooling of oral secretions, and the patient was placed in a tank respirator. She became shocked and did not respond to transfusions and intravenous noradrenaline. The temperature rose and suddenly large amounts of bright red blood gushed from the tracheotomy tube and the patient died. Autopsy revealed that the immediate cause of death was hemorrhage into a bronchus, secondary to perforation of the lower end of the esophagus. The diagnosis of poliomyelitis was confirmed histologically.

Autopsy summary on the male fetus: This fetus, which was almost at term, was removed via an abdominal incision, in the autopsy room. There were no pathologic changes in the nervous system. There were large subepicardial and subpleural hemorrhages and evidence of fetal pneumonia. There was no gross or pathologic evidence of poliomyelitis.

Type 1 poliomyelitis virus was isolated from the meconium. No virus was isolated from cord blood.

CASE 3.—A patient who was eight and one-half months pregnant on admission was in severe respiratory distress. She had complained of sore back, headache, stiff neck, and sore throat for the past three days. She was immediately placed in a tank respirator, but because of excessive pooling of oropharyngeal secretions it was necessary to do an emergency tracheotomy. In spite of supportive measures the patient became comatose, had a marked drop in blood pressure and gross hematemesis, and died two days later. No examination of the central nervous system was allowed.

Autopsy summary on the male fetus: A full-term male fetus was removed in the autopsy room via an abdominal incision. There were no changes in the central nervous system. There were numerous subpericardial,

subendocardial, and subpleural hemorrhages. There was no gross or pathologic evidence of poliomyelitis. Type 1 poliomyelitis virus was isolated from meconium. No virus was isolated from cord blood.

CASE 4.—A 25-year-old female was admitted at term on Aug. 5, 1953. There was a history of weakness and malaise for four days, and stiff neck and headache for three. On admission there was extensive paralysis of all limbs and marked weakness of the intercostal muscles.

CASE 5.—This woman, who had also reached term, was admitted on Aug. 3, 1953. Her complaints were vomiting, headache, and stiff neck. Lumbar puncture yielded 77 white blood cells (90 per cent lymphocytes) and protein of 40 mg. per cent. She had a left facial paralysis and paresis of both legs. On August 9, she was delivered spontaneously of a full-term, normal male infant.

The newborn infant had an uneventful course, showed no signs of infection, and is well.

TABLE I. SUMMARY OF CASE REPORTS AND VIRUS STUDIES

CASE	CLINICAL TYPE OF POLIOMYELITIS IN MOTHER	ULTIMATE OUTCOME OF MOTHER'S DISEASE	NATURE AND TYPE OF DELIVERY	GROSS AND MICROSCOPIC FETAL PATHOLOGY	FETAL AND NEWBORN MECONIUM AND STOOL SPECIMENS	FETAL AND NEWBORN CORD BLOOD SPECIMEN
1	Spinal	Convalescent	Stillborn male, delivery via low forceps	No evidence of poliomyelitis	Positive for type 1 poliomyelitis virus	No virus isolated
2	Bulbar	Fatal	Male fetus delivered via transabdominal incision in autopsy room	No evidence of poliomyelitis	Positive for type 1 poliomyelitis virus	No virus isolated
3	Bulbar	Fatal	Male fetus delivered via transabdominal incision in autopsy room	No evidence of poliomyelitis	Positive for type 1 poliomyelitis virus	No virus isolated
4	Bulbar	Convalescent	*Normal delivery;* male, newborn alive and well	--	No virus isolated	No virus isolated
5	Spinal	Convalescent	*Normal delivery;* male, alive and well	--	No virus isolated	No virus isolated
6	Bulbar	Fatal	*Normal delivery;* female, alive and well	--	No virus isolated	No virus isolated

The patient was placed in a tank respirator immediately. The next day a tracheotomy was done, because of pooling of the oropharyngeal secretions. She was delivered of a full-term male infant on August 9. The mother is still confined to a tank respirator. The infant was normal at birth, showed no signs of poliomyelitis, and is alive and well.

The meconium and stool specimens from the infant showed no evidence of poliomyelitis virus. It was not possible to isolate the virus from this infant's cord blood.

No virus was isolated from the stool or cord blood specimens.

CASE 6.—The patient was 24 years old and was at term when admitted on Aug. 12, 1953. She had complained of drowsiness and muscular pains for five days, had a stiff neck, and vomited several times. The spinal fluid was clear but contained 205 white blood cells, and 40 mg. per cent protein. There was marked dyspnea and her vital capacity was 1,400 c.c. There was marked pooling of secretions, so the patient was placed in a tank respirator and a tracheotomy was done.

She was delivered of a normal female infant on August 16 and from that date on showed gradual deterioration, with fever, delirium, and stupor. The patient died Aug. 25, 1953. Postmortem examination was refused.

The newborn infant was normal at birth and is alive and well. No virus was isolated from the stool or cord blood specimens in this case.

The results are summarized in Table I.

DISCUSSION

Poliomyelitis is rarely diagnosed in the first year of life.[12] It is particularly rarely recognized during the neonatal period.[13, 14] It is probable that cases of infection in infants are missed in the absence of virus studies. This view is upheld by our own findings, in which the presence of poliomyelitis would not have been made known without special virus studies. Since viremia has been shown to occur in poliomyelitis, transplacental infection has seemed plausible. The finding of the virus in the meconium of these stillborn infants of mothers with poliomyelitis would appear to be a clear demonstration of intrauterine infection, since the possibility of contamination of the meconium with virus seems remote. Clear-cut evidence for intrauterine infection has been presented by Schaeffer and co-workers,[7] who isolated the type 1 poliomyelitis virus from placenta and fetus of a mother with this disease. Swarts and Kercher[8] also described a fatal case in which type 1 virus was isolated from the central nervous systems of both mother and child. Shelekov and Habel[15] have described a case in which the healthy baby showed no clinical sign of poliomyelitis. Type 1 poliomyelitis virus was isolated from meconium and rectal swabs of the baby and from the placental villi. There was a low titer of type 1 antibodies in the cord blood at delivery, but antibodies were present in high titer in the child's blood one month later.

These reports in the literature and our own findings demonstrate that intrauterine infection with poliomyelitis does occur, and they add support to the concept that viremia is a feature of the pathogenesis of poliomyelitis.

SUMMARY

1. Poliomyelitis virus was isolated from the stools of three stillborn infants of mothers with acute poliomyelitis.

2. The evidence for transplacental transmission of poliomyelitis is reviewed briefly.

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On Pyloric Stenosis

The Child was five months old and was so emaciated that he appear'd rather to have decreased than to have encreased in Bulk from the time of his Birth, the whole Body not weighing above five Pounds. The Skin and Muscles of the Abdomen were very thin, but the Peritoneum was preternaturally thick. The Ventriculus was more like to an Intestine than to a Stomach its length being five inches and its breadth but one inch. The Coats of it were thick and fleshy, and the cavity very inconsiderable. The Pylorus and almost half the Duodenum were cartilaginous and something inclined to an ossification, so that no nourishment could have passed into the Intestines tho' the Stomach had been capable of containing it, which makes it no wonder that the Body was so emaciated.

There were scarce any footsteps of the Omentum to be seen even at the Bottom of the Stomach to which it usually adheres. The Right lobe of the Lungs adhered firmly to the Ribs and had three Exulcerations which contained purulent Matter. It was so very thin and compact that it seem'd as if that Lobe had never been of use in Respiration, the left Lobe was of a more florid Red, spongy and free from any Adhesion.

Upon enquiring after the Symptoms this Child had been affected with, his Mother told me he seem'd to be healthy till he was about a Month old, when he was seized with a violent Vomiting and a Stoppage of Urine and Stool. Some time after both these became more regular, but the Vomiting still continued. He seem'd to have a great Appetite, taking what Suck, Drink, or other Food was offer'd him with a kind of eagerness but he immediately threw it all up again.

PATRICK BLAIR, 1717.

Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

THIS 11-month-old white male infant was admitted to The Children's Medical Center because of drowsiness for one week. The patient had been in apparently good health until one week prior to entry, when he became drowsy, irritable, and feverish. The symptoms increased despite phenobarbital, given for "teething." The highest recorded temperature was 100.2° F. No vomiting, convulsions, or skin rashes were noted. The infant had been eating well.

Six months prior to entry, following an episode of "virus pneumonia," the mother had been admitted to a sanatorium for pulmonary tuberculosis, with a positive sputum. A patch test on the infant, a month following her admission to the sanatorium, was positive. Since that time he has had several chest roentgenograms which showed "shadows on the lungs." No specific antituberculous treatment had been given.

The infant's health has always been excellent. He sat at 6 months of age and walked with help at 11 months. Thirteen days prior to admission he bumped his head on a radiator, with no observable ill effects.

The physical examination on admission revealed a temperature of 100.2° F., a pulse of 120 per minute, and respirations 20 per minute. The weight on admission was 20 pounds. The patient appeared chronically ill, irritable, and listless, but in no distress. Evidence of recent weight loss was present. The head circumference was 46.5 cm. The anterior fontanel was full and slightly bulging. The neck and back were slightly stiff. A tonic neck reflex was present on the left. The deep tendon reflexes were hyperactive, bilaterally. Hoffmann's sign was present bilaterally but no other pathological reflexes were elicited. A questionable weakness of the left leg was noted. The remainder of the physical examination was negative.

The initial examination of the urine revealed a 1 plus sugar and a 1 to 2 plus proteinuria; both these findings were persistently present. The urine sediment was negative. The examination of the peripheral blood revealed a hemoglobin of 11 grams per cent, a leukocyte count of 27,200 per cubic millimeter, with 58 per cent polymorphonuclears, 36 per cent lymphocytes, and 6 per cent mononuclear cells. On lumbar puncture the initial pressure was 260 mm. and the final pressure 90 mm. of water. The fluid obtained was clear but contained 250 leukocytes per

cubic millimeter, all of which were monocytes; many erythrocytes were present. The total protein was 59.2 mg. per cent and no sugar was found in a five tube test. A smear of the spinal fluid was negative for acid-fast bacilli, as were a culture and guinea pig inoculation. An old tuberculin test was positive at a dilution of 1:10,000. Three gastric washings were negative for tuberculosis by culture and guinea pig inoculation. The serum electrolytes were normal except for a sodium of 130 meq. per liter. A roentgenogram of the skull showed split sutures, while a chest roentgenogram revealed a right paratracheal and hilar lymph node enlargement and a thick, irregular opacity extending anteriorly to the base of the right upper lobe.

The patient was placed on streptomycin therapy at a dosage level of 55 mg. per kilogram, 250 mg. being given intramuscularly twice a day, and 25 mg. being given intrathecally the first day, and 50 mg. on the succeeding days. Para-aminosalicylic acid was given at a level of 0.5 Gm. four times a day.

For the first few days he ran a low-grade fever with elevation to 101° F. but took feedings well. On the seventh hospital day he developed a fever of 108° F. and a mottled, cyanotic skin. A ventricular tap done on the right side yielded 1 c.c. of clear fluid. After intravenous fluids were started, the temperature fell to 97° F. and he developed vascular collapse and Cheyne-Stokes respirations. Intravenous albumin, blood, adrenal cortical extract, 2 mg. of epinephrine hydrochloride, and intravenous infusion helped to maintain the blood pressure. He vomited guaiac-positive material four times. The peripheral blood hemoglobin was 6.9 grams per cent and the leukocyte count 37,000 per cubic millimeter. Because of the possibility of a superimposed pyogenic infection, penicillin (300,000 units) was given every four hours; vitamin K (2.5 mg. per day) for five days, and 125 c.c blood were also given. The peripheral blood hemoglobin on the ninth hospital day was 11 grams per cent.

Following this febrile episode, the child remained stuporous, with poor peripheral circulation. On the tenth hospital day, moderate generalized edema developed. Serum protein was 4.7 Gm. per cent, and 15 cm. of serum albumin was administered intravenously.

The cerebrospinal fluid pressure remained about normal throughout the early hospital stay, with no evidence of block. The sugar content began to rise on the fifth hospital day and remained normal thereafter. A lumbar puncture on the tenth hospital day yielded bloody fluid which did not clear. Three days later the fluid was still xanthochromic, but was free of blood cells subsequently. Intrathecal streptomycin was given every day for eleven days; thereafter, once every other day. The dosage of parenteral streptomycin was increased 100 mg. per kilogram per day on the twentieth hospital day.

During the last week of life the infant remained comatose. He was fed through an indwelling tube and vomited frequently in small amounts. The cerebrospinal fluid protein rose gradually to a high of 489 mg. per cent on the twenty-third day of treatment. This was accompanied by a drop in the cell count, with low pressure in the lumbar area. On the

twenty-fifth day the infant was found lifeless, two and a half hours after the last feeding, with dark yellow fluid coming out of the mouth.

DISCUSSION

DR. EDITH M. LINCOLN.*—Dr. Shwachman asked me if I would discuss a case of tuberculosis at this Clinical Pathological Conference, and I must confess I was rather surprised to find that it was going to be a case of tuberculous meningitis. We feel that tuberculous meningitis is now one of the less common problems in the field of tuberculosis. The problem of prevention of meningitis now looms large in all our minds. We see less and less meningitis and, as a matter of fact, we had our first case of tuberculous meningitis in over six months within the past week, our second in a year. Now, curiously enough, Dr. Berenberg tells me that you have as much as in the past and, if anything, a little more. I have heard of the same trend in New Haven. It just illustrates again, I think, the differences in the character of tuberculosis in children whom you see in different parts of the country and in different countries, in the clinical pictures presented and in the incidence of the various complications. I submit, however, that one of the reasons why we are seeing less meningitis in New York is that there is, on the part of the Department of Health, an intensive effort to treat as many outpatients as possible with isonicotinic acid. Knowing that isonicotinic acid has a very rapid effect in diminishing the number of bacilli in the sputum, I suspect that we are having fewer children heavily infected. A large number of children are being treated with this compound. Curiously enough, we are seeing just as much of the severe type of childhood tuberculosis as before, except for the meningeal variety. We have eight or nine cases of miliary tuberculosis on our ward at the present time, and only a single case of tuberculous meningitis.

In this particular case being presented, I think there are many points of interest. In the first place, this was a previously healthy 11-month-old baby who had a history of only one week of drowsiness. Of course, that is a classical history of the onset of the disease if we are privileged to see it in the really early stages. It is the early case that presents the greatest problem in differential diagnosis, and these same early cases are most important to diagnose and treat early. Everyone now believes that you can cure the great majority of cases of tuberculous meningitis if diagnosed in the early phase. At Bellevue, we have been able to cure 85 per cent of these patients, and not only do they survive but they rarely have any neurological sequelae. Therefore it becomes increasingly important to think of meningitis in a differential diagnosis as tuberculosis and tuberculous meningitis decrease in frequency in the community.

This child had the typical early symptoms of tuberculous meningitis. He was drowsy, he was irritable, and he was feverish. He had no history of vomiting or convulsion, which would be very common in a baby this age.

From the past history we learn that the mother has a proved case of tuberculosis, and that the baby has had known tuberculosis for five months.

*Dr. Edith M. Lincoln is Visiting Physician, Children's Medical Service, Bellevue Hospital, and Professor of Clinical Pediatrics, New York University College of Medicine.

The child had a positive patch test and a presumably positive roentgenogram five months before his hospitalization. The first six months after the discovery of a primary lesion is the most common time during which a child is likely to develop tuberculous meningitis. About 77 per cent of our meningitis cases which occurred before any therapy was available fell into that period, the first six months after the onset of the pulmonary disease. No treatment was given this infant. That is interesting because, of course, most of us have felt for many years that no treatment should be given to the child with an asymptomatic primary pulmonary tuberculosis, such as was present in this case. We are beginning now to feel that isonicotinic acid will definitely prevent meningitis. As many of you know, study of a randomized series, under the Public Health Service, will start within a few weeks and we hope to have a final answer to that question. But I think we can suspect already, from what we know, that if this child had been treated the chances are that he would not have developed meningitis.

Thirteen days before admission, this baby bumped his head on a radiator, with no observable ill effects. One always thinks, of course, of a possible precipitating effect of such an injury on the development of tuberculous meningitis. Most of us believe that there is usually a focus close to the meningitis, either in the brain or in adjacent areas, in which a tuberculous focus exists before the development of the meningitis. Then it is obvious that sometimes injury may play a part. However, it is striking, in the history of cases which have gone on to autopsy, that walled-off foci in the brain or meninges are more commonly found not in the child with an acute primary pulmonary tuberculosis, but in the child who has had primary pulmonary tuberculosis for some time with evidence of calcification. Those are the children in whom a walled-off tuberculoma is more likely to be found, which has broken down in some way and caused a meningitis. However, I do not think we can rule this possibility out entirely. This is another one of the factors which seem to differ greatly in different parts of the country. In Bellevue, for instance, the great majority of our cases of meningitis have evidence of primary pulmonary tuberculosis, and a high percentage of those are active pulmonary tuberculous infections without calcification. In Buffalo, Dr. Terplan says that the great majority of his cases of meningitis have primary lesions that are very difficult to find and are more often obsolete than fresh. I have heard that such differences exist in other parts of the country.

Now, in his admission physical examination, I think one of the striking things is the fact that his temperature was only 100.2° F. Even after a week of illness with meningitis, you usually see more fever than that. With the neurological finding that his anterior fontanel was full and bulging slightly, one thinks immediately of the possible presence of hydrocephalus. However, since the head circumference was normal, one would suspect that the bulging fontanel was one which is occasionally seen early in a meningitis, or that the child had been crying. Even though the other neurological findings are very marked, I think that except for suspected weakness of the left leg one could justifiably classify this child

as being in the first stage of meningitis. When a child is admitted with definite weakness or with hemiplegia, you know at once that he has been ill a great deal longer than a week. From a pathological standpoint, we think that most of these cases of definite hemiplegia are due to pressure on the corticospinal tracts, secondary to the pressure of the exudate at the base of the brain.

Some of the laboratory data are very easy to reconcile with the clinical picture of the child, and, on other points, not quite so easy. The positive urine sugar, on admission, I think is a little hard to explain; but the later ones, of course, when the child was getting intravenous fluid after the seventh day, are not surprising. The peripheral leukocyte count of 27,000, I think, is sometimes confusing; we do see high blood counts both in meningitis and in miliary tuberculosis. They are more likely to appear in a rapidly progressing case, but I do not remember seeing such an amount in a meningitis case where the temperature was only 100.2° F. The pressure in the initial lumbar puncture had an opening figure of 260 mm. of water and a closing pressure of 90. That, of course, immediately rules out the possibility of blockage of the cerebrospinal fluid pathway. I do not know whether it is customary for you to sedate your patients before doing the lumbar puncture—because if this child was sedated, then 260 mm. of water is a very high initial pressure, but in an unsedated child it is just really a high normal.

DR. MAURICE OSBORNE.—We do not do so, customarily.

DR. LINCOLN.—The spinal fluid removed was characteristic of many cases of tuberculous meningitis, showing pleocytosis (205 cells per cubic millimeter in this case—all mononuclears) and a total protein of 59 mg. per cent, which again speaks against the possibility of a block in the cerebrospinal pathways. The sugar, however, is low. There was no reduction in five tubes; we usually feel that this means less than 10 mg. per cent of sugar. We think this implies a poor prognosis and it is not uncommonly seen in the first specimen. A low sugar, which then proceeds to fall further, has occasionally been seen in fulminating cases. The fact that no laboratory work proved the cultures to be positive is always a factor against the diagnosis, but every laboratory occasionally has periods in which the negative findings are frequent, without explanation. I do not know why the serum sodium was low. There is not any obvious explanation for it, unless we can relate it to the collapse which took place on the seventh hospital day. He had obviously had no x-ray signs of pulmonary tuberculosis.

His skull films show the presence of split sutures. I do not know quite whether that means the normal split sutures which you might find in a child of 11 months, or whether there was actual separation of the sutures. You have no other evidence of the presence of a hydrocephalus or a block in this child on admission or in the first week of his illness.

This child was treated, of course, before the time when isonicotinic acid was used, and I do not know why he was treated with less than 100 mg. of streptomycin per kilogram. He also received intrathecal treatment. We have not used any intrathecal therapy

for about two years. We find that results are just as good or better than they were with the intrathecal administration. That, of course, is due entirely to the addition of isonicotinic acid to our treatment schedule. No isonicotinic acid was used here, so I think you had to use the intrathecal streptomycin.

Now what happened to this child on the seventh hospital day is something that I hope Dr. Farber will be able to throw some light on. He developed a fever after having had a low-grade fever. He developed a mottled, cyanotic skin and went into circulatory collapse. That sounds as if he had an acute adrenal insufficiency, because he had high fever; he had peripheral collapse and he had a low sodium, although I do not know whether you can relate that sodium (which I gather was taken on admission) to what happened on the seventh hospital day. The other thing one thinks of as a possibility is the rare occurrence of herniation of the brain, which might be due to increased local pressure from the exudate, and which might cause the high fever and the collapse. The possibility is ruled out by the ventricular tap, which yielded only 1 c.c. of clear fluid. In a herniation of the brain, one would have found a very high ventricular pressure with a large amount of fluid. He apparently responded to the treatment for acute adrenal insufficiency.

He developed a generalized edema and I would be very happy to know why some of these children do this. We have seen children with various types of electrolyte disturbance in our meningitis series develop a generalized edema and we have not been able to combat it successfully. Obviously the bloody cerebrospinal fluid, I think, can be explained only on the basis of the traumatic tap, because apparently the fluid did clear subsequently and remained free of blood. The child developed a lumbar block late in the course of his disease. He had the characteristic picture of a high protein content of the spinal fluid (489 mg. per cent), a drop in the cell count, and very low pressures in the lumbar area. I do not know what the exact cause of death was, because I am never sure exactly why children with tuberculous meningitis die. They may die of toxemia, they may die of hydrocephalus—but the exact mode of death is always a problem. I think, then, we have a child who had a primary pulmonary tuberculosis, who should show caseous, tuberculous primary and regional nodes, and who probably will show some hematogenous scattering in various organs, probably in his spleen and liver, but not an acute generalized miliary tuberculosis. He will probably show a tuberculous meningitis with a spinal block. He may show hemorrhages or caseation in his adrenals but may show no abnormality there at all.

Dr. James Baty.—Were subdural aspirations done at the time of the ventricular tap? I wondered about the possibility of a hematoma or hemorrhage that might account for this child's not responding to treatment. As Dr. Lincoln points out, the treatment may have been inadequate, which might account for its failure.

Dr. Osborne.—No separate explorations were made of subdural spaces.

Dr. Farber.—Dr. Lincoln, how do you handle the situation in a child who does not have this good evidence of

active pulmonary tuberculosis—where everything seems to point to tuberculous meningitis, but you can't find the evidence in the spinal fluid? Would you be willing, if the child had only a positive tuberculin test, as sometimes happens, without the isolation of the organism, to proceed with treatment?

DR. LINCOLN.—I think that with such a characteristic spinal fluid, you should be willing to go ahead. A very low spinal fluid sugar like that occurs in very few lesions. It does not occur in the viral infections, usually, although it may occur in the purulent meningitides; but you should be able to diagnose these very speedily. Low spinal fluid sugars may occur occasionally in malignancy and a very low sugar in a rapidly developing malignancy—yet there are few conditions that would give you a sugar below 10. It is better to treat a patient for tuberculous meningitis, since you can cure a large percentage of them, than it is to withhold therapy until you can be absolutely sure of the diagnosis.

DR. JACK METCOFF.—The low serum sodium values in tuberculosis, and I presume also in tuberculous meningitis, have excited considerable interest in recent years. Studies have suggested one or two possible etiologies for this: one was that the total amount of sodium normally present in the extracellular fluid was decreased, and the other, that there was an increase in extracellular fluid without a significant change in the total body water. Recent studies on distribution of chloride in this situation in children suggest that there is a marked increase in the extracellular fluid or chloride space. If this is so, it might explain, in part, why edema might very well occur in a later phase of therapy, and this in association with an apparent reduction in the amount of electrolytes present in the fluid.

Another comment that I would like to make is in relation to the two hemoglobin values which we are given: the first, 11 grams per cent at admission, and the next, 6.9 grams per cent after the episode of shock. Very quick arithmetic, on the assumption that the blood volume had been restored after collapse, suggests that there had been a loss of about 300 c.c. of blood. I am curious to know where this loss might have occurred. We are told that part of it came, apparently, from the gastrointestinal tract.

DR. FARBER.—Dr. Wittenborg, would you show the x-rays?

DR. MARTIN H. WITTENBORG.—We have only one chest examination. There is a definite parenchymal, infiltrative lesion in the right mid-lung field, with some reaction in the minor pleural fissure, and a true hilar lymphadenopathy on the right. I think it is only fair to say, Dr. Lincoln, that without prior knowledge of the history, on viewing the lateral skull, I think that the sutures are definitely separated and the fontanel is bulging.

DR. WILLIAM BERENBERG.—Dr. Lincoln asked a few questions with regard to some of our local practices which I might try to answer at this point. I was delighted to hear Dr. Lincoln discuss hemiparesis, because in our experience hemiplegia has been pretty common. I am intrigued with her explanation that it is a manifestation not seen in the first week. We are rarely privileged to see patients

in the first week. Most of our patients enter the hospital in the second or third week of their disease and our incidence of hemiplegia in this type of meningitis has been extraordinarily high. With regard to the frequency of positive chest films, 85 per cent of all our patients with meningitis have had positive parenchymal involvement demonstrable by x-ray. Dr. Lincoln is quite right in criticizing our dosage of streptomycin; it was corrected on the twentieth day. We have always urged that people use 100 mg. per kilogram, and I imagine what happened was that someone confused the dosage which we ordinarily use in straightforward pulmonary involvement without miliary or meningeal involvement, and started at 5 mg. lower dosage. We have discontinued using intratheeal streptomycin within the last several months and we are in perfect agreement on the value of isonicotinic acid.

DR. WILLIAM CHEATHAM.—The autopsy findings were those of pulmonary tuberculosis, tuberculous meningitis, and extensive encephalomalacia of the cerebral hemispheres. There was an area of retroperitoneal hemorrhage in the right lower quadrant, but this was not enough to account for the blood loss which Dr. Metcoff calculated, nor did we find any other evidence of bleeding. There were several well-localized (0.5 to 0.7 cm.) areas of caseation in the right middle and left lower lobes of the lungs. The hilar nodes, bilaterally, were enlarged up to 2 cm. in diameter, and caseous. The liver had a moderate degree of central

Fig. 1.—Photomicrograph, kidney. The tubules are dilated and contain casts. (Hematoxylin and eosin; ×170; reduced ¼.)

lobular necrosis. The adrenals were anatomically normal. The kidneys were slightly enlarged and had pale cortices. Microscopically, they contained casts in the distal convoluted tubules, with considerable regenerative activity here. (Fig. 1.) These were interpreted as a healing stage of "lower nephron nephrosis" and were thought to be related to the period of shock noted on the seventh hospital day.

There was an extensive tuberculous meningitis and widespread caseation necrosis of the brain. In addition there was a massive encephalomalacia involving the left frontal and parietal lobes, and the basal ganglia of each cerebral hemisphere (Fig. 2). This extensive softening of the brain was thought to have its origin in part in the widespread obliterating endarteritis of the meningeal cerebral vessels. Some had been thrombosed and showed recanalization (Figs. 3 and 4), while others had necrosis of the walls and were only recently undergoing thrombosis. No tuberculoma was present, and no pressure cone could be demonstrated. The cause of death was believed to be related to these vascular lesions and the resulting massive brain destruction.

Fig. 2.—Cross section of the brain. There is extensive encephalomalacia of the parietal lobes and basal ganglia. There is considerable caseous exudate about the branches of the middle meningeal arteries (at arrows).

DR. CRAIG.—I believe such arterial lesions as were present in this case are being found in increased numbers over those found before 1940.

DR. FARBER.—That may be true; but we have seen, over the years, and even before the days of the use of effective chemotherapy, arterial and periarterial inflammation associated with tuberculous processes in the meninges, but less

Fig. 3.

Fig. 4.

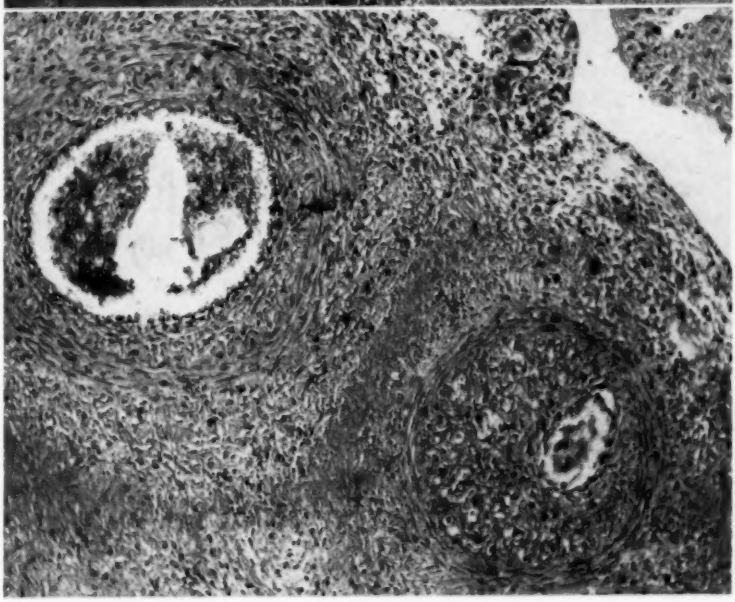

Fig. 3.—Photomicrograph, brain. There is marked exudation and caseous necrosis about the branches of the middle meningeal arteries which are in various stages of occlusion. (Hematoxylin and eosin; ×40; reduced ⅛.)

Fig. 4.—Photomicrograph, brain. The proliferative nature of the endothelial reaction giving rise to vascular occlusion is seen. (Hematoxylin and eosin; ×40; reduced ⅛.)

frequently related to thrombosis. Such arteritis lesions have always been commonly associated with massive softening of the brain.

I agree with Dr. Cheatham that we would not expect to find a tuberculoma in such massive softening, but even in the instances where there was definite meningitis without massive softening we have had a very poor yield of primary tuberculomas or of important tuberculomas at the point of seeding of the meninges.

DR. LINCOLN.—We have had much more experience, of course, before effective therapy was available; and then we had a fairly high percentage of tuberculomas or tuberculous foci in adjacent areas, such as the mastoids. I think, as Dr. Farber says, that there always have been some arteritis and areas of softening in cases of tuberculous meningitis. We have to remember that the average duration of a tuberculous meningitis before therapy was about nineteen and a half days from the time that it was diagnosed, and that, therefore, such late developments were relatively infrequent. I think it is only since treatment has prolonged the life of the child with tuberculous meningitis that we are seeing such a high percentage of cases of arteritis and encephalomalacia.

DR. FARBER.—I think that is probably the explanation.

DR. LINCOLN.—I might comment on the decrease in meningitis in relation to what we saw in the past. Since 1922 we have not varied by more than two or three in the yearly number of cases of tuberculous meningitis that we have had, until three years ago; and in the last two years we have had about one fifth of the number of cases that we have had previously—a sharp drop.

DR. FARBER.—Is there any correlation with the changes in the neighborhood around Bellevue?

DR. LINCOLN.—No, I would say that, if anything, we are drawing a younger group of patients. We formerly had a great many patients up to the age of 8 or 12, and now 70 per cent of our patients are 3 or under. We have more Negro and Puerto Rican patients, who normally, one would think, would have a higher incidence of meningitis.

Comments on Current Literature

SEVERE INFECTIONS IN SPLENECTOMIZED INFANTS AND CHILDREN

THE spleen in some respects still remains an organ of mystery; however, recent developments in the field of hematology have brought about a better understanding and a more satisfactory classification of the blood dyscrasias in their relation to the spleen. Increased knowledge of splenic function has served to refine the indications for splenectomy. Indications and contraindications for splenectomy with their qualifications were summarized in a review article by Sanders and Kinnaird[1] in 1956: ". . . trauma to the spleen heads the list of indications for splenectomy both in urgency and frequency. Fifty-five years of clinical trial and error have shown that idiopathic thrombocytopenic purpura and hereditary hemolytic anemia share the honors in scarcely subordinate fashion to trauma as prime indications for splenectomy."[1] In Banti's disease and splenic anemia, indications for splenectomy require individual evaluation, "so that today, splenectomy is rarely advocated for 'splenic anemia' and splenomegaly in the absence of significant hemolysis or hypersplenism, and is avoided in Banti's syndrome except as a part of a vascular shunting procedure."[1]

In a recent clinical study Carl H. Smith and his associates[2] point out that, while increasing experience with splenectomy has emphasized the therapeutic value and relative safety of this procedure, attention should be focused on an appreciable number of recorded cases in which serious, recurrent or fatal infection has occurred in the splenectomized patient. In this article, which appears in the *American Journal of Medicine* for March, 1957, Smith, Erlandson, Schulman, and Stern[2] refer to the cases recorded in the literature, two of which were their own, and extend their "initial observation indicating a heightened susceptibility to severe infection in a group of infants and children in whom the spleen had been removed for a variety of conditions mostly of a hematologic nature."[2]

Findings on nineteen cases, six of which terminated fatally, are given in this report, the cases falling into several categories: "those associated with meningitis, acute pericarditis and sepsis, and a group consisting of acutely ill children in whom the course was so fulminating as to preclude the detection of a specific etiologic agent." Case histories on all nineteen patients are summarized; complete laboratory studies were not always possible for the fulminating cases, some of the patients having died a few hours after admission.

The previous publication by Smith and his colleagues[3] concerned a study of Cooley's anemia; two of the children reported experienced an overwhelming fatal illness with high fever, prostration, and coma, sixteen months and two weeks, respectively, following splenectomy performed for Cooley's anemia. Examination of the literature at that time by these authors revealed other recorded cases, notably five infants under the age of 6 months with congenital spherocytic anemia reported by King and Shumacker[4] in 1952. In four of these five infants fulminating infection, either meningitis or

meningococcemia, developed within five weeks to three years after splenectomy, and one of the five children died a few days after discharge following surgery from a rapidly fatal febrile illness of unknown etiology.

In the nineteen cases presently reported by Smith and his associates, the range in age was from 2 to 17 years, some of the patients experiencing repeated episodes of severe infection over a period of years. These authors include case histories, tabular information concerning time relationships, indication for splenectomy in their own and recorded cases, and an analysis of the type of infection, as well as a discussion of the spleen's contribution to natural resistance and body defenses. The infections fall into a number of well-defined groups: meningitis (seven cases), acute pericarditis (five), acute endocarditis (one), sepsis (three) and three acutely ill patients in whom the course of the infection was so fulminating that specific etiologic detection was not possible. In eleven of the cases bacteriologic diagnosis was accomplished, pneumococcus being the most frequent offender (six cases). Other organisms incriminated included *Escherichia coli* (two cases), *Salmonella typhimurium* (one case), alpha streptococcus (one), and *Hemophilus influenzae* (one). In the meningitis group of patients pneumococcus was the predominant organism, isolated in five of seven cases of meningitis. In one of the patients with meningitis recurrent attacks occurred which were caused by different strains of pneumococcus. This situation also obtained, as the authors point out, in some of a group of patients reported by Gofstein and Gellis[5] in 1956.

A study of the individual case histories in these nineteen cases revealed that in most instances an apparently well child became seriously ill after a short prodromal period. In a few instances the child had been somewhat susceptible to recurrent infection before splenectomy; in some patients, notably those with meningitis, the fulminating clinical features followed several days of illness during which antibiotics were administered with apparent improvement. Pericarditis occurred in eight instances: eight attacks in five children, all of whom had severe Cooley's anemia; no specific etiologic agent could be identified. Clinical manifestations and laboratory findings were compatible with the recognized features of acute benign or idiopathic pericarditis which have been described in adults. Each of these patients experienced substernal pain which appeared to be sudden and intense across the upper and lower anterior chest radiating to the back and shoulders. The pain was aggravated by breathing or motion and was somewhat relieved by the sitting position. Leukocytosis, fever, and pericardial friction rub with some evidence of effusion were prominent findings. The electrocardiogram showed characteristic changes. Tendency for this condition to recur was apparent in two cases, one patient suffering two and the other three such attacks, followed in every instance by recovery.

The major indication for splenectomy in these cases was referable to conditions associated with an established blood dyscrasia, and the procedure was undertaken as a means of reducing transfusion requirements and improving patient status. The interval between the surgical procedure and infection ranged from one day to twelve years, with the majority of episodes (80 per cent) occurring within two years or less. The shortest periods (24 hours and 13 days) were in two patients with fulminating course and fatal outcome. In two of the children, each 6 years of age, splenectomy was carried out because of traumatic rupture of the spleen. From the standpoint of infection susceptibility in relation to splenectomy, these two essentially normal children are of special interest. One of them experienced two episodes of pneumococcal meningitis (type 23 and type 12) in a period of eighteen months

postoperatively, and the other alpha streptococcal sepsis at 1 year following removal of the spleen. Both patients recovered.

Electrophoretic studies of serum proteins were carried out in the case of eight of these splenectomized patients, and no diminution in the concentration of gamma globulin was detected, suggesting that the lowered resistance to serious infection following splenectomy was not associated with a deficiency in serum gamma globulin. In this connection the authors discuss the rather extensive clinical and experimental evidence concerning the contribution made by the spleen to defense mechanisms of the body. They quote from the Ludwig Kast Lecture given by Dubos[6] before the New York Academy of Medicine in 1954, which deals with the biochemical determinants of infection: ". . . many types of substances, procedures or accidents have been found capable of bringing about conditions under which latent microorganisms can manifest their potential pathogenicity and cause overt disease."

While the number of pertinent cases recorded is relatively small in proportion to the over-all number of splenectomies performed, these authors suggest that the few are of considerable significance, and that removal of the spleen may very well foster vulnerability to infection. In addition to clinical observations such as theirs, extensive experimental evidence "implicates the spleen in fundamental processes relating to resistance to infection."[2] Thus in summary, they emphasize that "the young splenectomized patient requires close supervision for several years postoperatively so that immediate and energetic treatment may be instituted in the event of sudden or severe illness."[2]

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

We were exceedingly interested in the article by Dr. Soifer on "Aminophylline Toxicity" and the comments concerning aminophylline by Drs. Glaser and Berman.

It may be of interest to cite that three cases of aminophylline toxicity were reported to the New York City Poison Control Center: one in 1955, one in 1956, and another in 1957.

1. The first case was in a male child, 2 years of age, who in a period of twenty-four hours prior to the onset of symptoms was administered four ¼ Gm. suppositories, a total of 1 Gm. aminophylline suppositories. The symptoms were vomiting, lethargy, and dehydration. The child was taken to the hospital where the stomach was lavaged and intravenous fluids were administered. He remained in the hospital for several days and made a complete recovery.

2. The second aminophylline poisoning was reported in a 10-year-old male child who had been given rectal instillations of aminophylline regularly for a period of ten months, but who was given two instillations a day for two months prior to the occurrence (5 grains of aminophylline powder dissolved in two or three ounces of water).

Dr. Joseph Dolgin, who reported the case, stated as follows:

"The child had been well all day on Thursday, Nov. 8, 1956. However at 9:30 P.M. he suddenly became confused and asked his father 'What day is this? Where am I?' He then seemed unsteady in his gait and began to reel. His father led him to a chair. The child very soon lost consciousness and fell into a deep coma. When first seen by me at 9:45 P.M., Thursday, Nov. 8, 1956, at his home, the child was in deep coma and showed frequent involuntary twitching of his facial musculature, which soon became generalized. He was then taken to the Staten Island Hospital. At the hospital he was given 1 grain of sodium Luminal intramuscularly and 3¾ grains of sodium Amytal intravenously. This brought his convulsions under control. He was given an infusion of 5 per cent glucose and saline and a hypodermic injection of caffeine and sodium benzoate, 2½ grains.

"The following morning the child was drowsy but conscious and at 10 A.M. was able to take fluids by mouth and speak coherently. He was discharged on Nov. 11, 1956—alert, cooperative, and neurologically negative. Impression: acute aminophylline poisoning."

3. The third aminophylline poisoning involved a 2½-year-old male child who accidentally ingested aminophylline. The child found a medicine bottle which was placed on the top of the sink in the kitchen. He climbed up on the chair, obtained the medication, and ingested an unknown quantity of aminophylline tablets. Each tablet contained 1½ grains of aminophylline. Though the child did not appear too ill, he was taken to a hospital where his stomach was lavaged and penicillin was administered. After a stay of three days in the hospital the child was sent home.

Is it possible that the ill effect from aminophylline may be due to the ethylenediamine which is an alkaline irritant? This preparation is just a molecular combination of ethylenediamine and theophylline.

Would it not be desirable to prescribe a theophylline preparation other than aminophylline?

In addition to the three cases which we cited above, we were also notified of a 13-year-old male asthmatic child who was given Tedral therapeutically and who experienced nausea, vomiting, and abdominal pains after the administration of Tedral.

It is recommended that parents obtain specific instructions from the physician in regard to the administration of aminophylline at the beginning of an attack, even though such preparation may be available in the home.

Physicians may also be reminded not to order aminophylline preparations in excess of the immediate need and that families should be instructed to keep all such preparations securely away from children and under lock and key.

HAROLD JACOBZINER, M.D.

News and Notes

At the 67th Annual Meeting of the **American Pediatric Society** held at Carmel, California, June 17 to 19, 1957, the following officers were elected for 1958:

President: Dr. A. Ashley Weech
Vice President: Dr. Alton Goldbloom
Secretary-Treasurer: Dr. Aims C. McGuinness
Recorder-Editor: Dr. Stewart H. Clifford

Member of the Council:

For a seven-year term: Dr. Edward L. Pratt

The following were selected to membership:

Dr. Robert H. Alway, San Francisco, Calif.
Dr. John B. Bartram, Philadelphia, Pa.
Dr. Alfred M. Bongiovanni, Philadelphia, Pa.
Dr. David H. Clement, New Haven, Conn.
Dr. Wallace W. McCrory, Philadelphia, Pa.
Dr. Gerald Miller, Rochester, N. Y.
Dr. Rosa Lee Nemir, New York, N. Y.
Dr. Edward F. Rabe, Danville, Pa.
Dr. Helen Reardon, Philadelphia, Pa.
Dr. Harry Shwachman, Boston, Mass.
Dr. Henry K. Silver, New Haven, Conn.
Dr. Genevieve Stearns, Iowa City, Iowa.

The John Howland Award was presented to Dr. Ethel C. Dunham.

The meeting in 1958 will be held at Hotel Traymore, Atlantic City, N. J., beginning Thursday morning, May 8.

Dr. Frank Bell Magill, pediatrician at the Children's Medical Center in Boston, and Mrs. Magill, who is a social worker and teacher, have been appointed to the McCord Hospital, Durban, South Africa, by the American Board for Foreign Missions of the Congregational Christian Churches. Founded a half century ago, the McCord Hospital was the first medical center for Africans in Natal.

Columbia University College of Physicians and Surgeons is offering *Postgraduate Cerebral Palsy Courses* for 1957-1958. An interdisciplinary approach to cerebral palsy is presented through lecture, clinical affiliation, and discussion seminar. Representatives of differing clinical methods are invited to demonstrate the practical application of their theories. Students are encouraged to acquaint themselves with all techniques, weighing the contribution of each to the needs of specific patients. There is ample opportunity to question authorities in the field, to exchange experience, and to apply critical thinking toward the development of a dynamic approach to the problems involved in therapy. The first three weeks are devoted to lectures and demonstrations on Medical Management (53 hours), Basic Science (22 hours), Psychosocial Aspects (13 hours), and Organization (2 hours). *Physicians' course:* 3 weeks full time, Oct. 14–Nov. 1, 1957; March 3–March 21, 1958. Includes lectures and demonstrations plus five days in cerebral palsy facilities with opportunity for discussion with the physician in charge. *Therapists' and Nurses' course:* 9 weeks full time, Oct. 14–Dec. 13, 1957; March 3–May 2, 1958. For occupational, physical, speech therapists, and rehabilitation nurses with proper qualifications and experience. For further information write Postgraduate Course in Cerebral Palsy, Office of the Dean, College of Physicians and Surgeons, 630 West 168th St., New York 32, N. Y.

Books

Clinical Toxicology of Commercial Products. Marion N. Gleason, Robert E. Gosselin, and Harold C. Hodge, Baltimore, 1957, Williams & Wilkins Co., 1,160 pages. Price, $16.00.

The authors, from the departments of pharmacology of the University of Rochester and the Dartmouth University medical schools, have written an encyclopedic volume on acute poisoning, which will become a standard book of reference. Its purpose is to present the toxic ingredient in thousands of articles, such as medicines, insecticides, cleansing agents, and the like, which are found in the home or on the farm and which may be accidentally ingested. In addition, the specific treatment is included. It is estimated that about eight fatal cases from swallowing some substance occur in the United States every day, as well as several hundred nonfatal cases of poisoning.

The amount of material in the book is tremendous, and obviously many thousand hours of work were involved in its preparation. The authors, moreover, have succeeded in presenting this material in a useful, practical way. There are seven sections, and four different colors of paper have been used, which aids materially in the usefulness of the book. Section I (14 pages) takes up first-aid and emergency treatment. This is followed by a section entitled "Ingredients Index," listing alphabetically over 1,000 chemical substances found in commercial products. Each is given a "toxicity rating" of from 6 (super toxic) to 1 (practically nontoxic). Section III (78 pages) presents the symptomatology and treatment of sixty-eight compounds or classes of compounds: acid, alcohol, aliphatic thiocyanates, or alkali, for example. This is followed by a short chapter on supportive treatment. Section V, "Trade Name Index," makes up the bulk of the volume (over 800 pages). Here some 15,000 products are listed by their trade names and their categories are indicated. For the majority they give the ingredients, with the toxic ingredient indicated by an asterisk. Two shorter sections complete the book, one on "General Formulations" and the other listing the manufacturing firms with their addresses.

The text enables a physician, when confronted with the story that some commercial product has been accidentally ingested, to ascertain without delay whether the product is toxic, what substance in the product is toxic, and the *degree of toxicity*, and to institute the correct treatment to counteract the poisonous substance. If the ingredients are unknown, the type of the product and its use will give an important clue.

It is a reference book that should be in every hospital and outpatient clinic, and in the library of physicians to whom emergency hospital service is not available.

B. S. V.

Modern Therapy in Neurology. Edited by Francis M. Forster, M.D., St. Louis, 1957, The C. V. Mosby Co., 792 pages. Price $12.00.

This text, which has been edited by Dr. Forster and to which some twenty men have contributed, is unique, as most neurological texts approach the subject from a descriptive standpoint, with little attention to treatment. The many advances that have been made in recent years in the treatment of diseases of the central nervous system and peripheral nerve lesions have been contributed to by workers in many fields, particularly the immunologist, the pharmacologist, and the neurosurgeon. Some of the subjects forming chapters in this book are today rarely thought of as "neurological diseases," but rather as "infections." Thus such subjects as those of the chapters on the treatment of meningitis, by Sahs, and poliomyelitis, by Baker,

are well covered in the standard texts on internal medicine, pediatrics, and infectious diseases. Other chapters, like the treatment of myasthenia gravis, by Eaton, and the management of degenerative and developmental disease, by Auth, belong more directly to the subject. The text, however, brings together that which has been learned in recent years regarding the treatment of diseases of the central nervous system and the big gaps still present in our therapeutic knowledge.

BCG Vaccination Against Tuberculosis. S. R. Rosenthal, M.D., Boston, 1957, Little, Brown and Company, 389 pages. Price $7.50.

Although it is estimated that over 100,000,000 have been vaccinated against tuberculosis by the BCG method, it has had limited use in the United States. Dr. Rosenthal's book takes up the history, preparation, and use of the vaccine, along with the related questions of immunization. One of the most interesting chapters is the early history by Dr. Guerin, who with Calmette developed the bacillus after years of painstaking research. As BCG vaccination is recommended in this country for groups particularly exposed to the disease, such as medical students and nurses, the book is of practical interest to physicians. Dr. Rosenthal has carefully culled out the important material on a subject that has many thousand references in medical literature. The possibility of prophylaxis being produced by some of the drugs introduced in the last few years is now being studied. Even if this should prove successful, the story of BCG vaccination will survive as a brilliant example of what can be accomplished by medical research. Dr. Rosenthal does not go into the use of BCG vaccination for leprosy which is presently interesting many public health scientists.

Chirurgie. Urgences chirurgicales neonatales. M. Dubois and G. Laurence. Les hernies hiatles by P. Hillemand, J.-L. Lortat-Jacob, R. Viguié, Y. Barré, and H.-J. Bernard, Paris, 1957, Masson & Cie, 96 pages. Price 1,100 francs (Fr.).

One of a series of brochures by members of the Faculté de Médecine de Paris. This discussion of neonatal surgery presents first a rather brief discussion of the surgical emergencies of the newborn infant: imperforate anus, intestinal obstruction, esophageal atresia, omphalocele, and spina bifida. A second chapter discusses the conditions necessary for successful surgery on the newborn child, and the results. In a discussion of results, the authors quote the figures of Gross of Boston, as "Les centres français ont une experience trop limiteé, à cause de leur jeunesse . . . "

The second part, which discusses hiatal hernias, is more interesting, with a number of excellent roentgenograms.

Kenny Visits the Hospital. Julia A. Bartosh, R.N., New York, 1956, Exposition Press, 62 pages. Price $2.50.

A Visit to the Hospital. Francine Chase, New York, 1957, Grosset & Dunlap, 68 pages. Price $1.50.

Miss Bartosh's text differs somewhat from the usual run of books and brochures on preparing the child for the hospital which have been appearing in the last few years. In reality, Kenny's visit is used to hang a picture of the various hospital services, instruments used, operating room procedures, the laundry, and the like. The story is told in excellent photographs with captions. It is an illustrated text of what goes on in a hospital, rather than the story of Kenny and the experiences he will meet. It should be of interest to adults and older children in health classes in the schools.

Miss Chase's book was prepared under the supervision of Dr. Lester L. Coleman, an ear, nose, and throat specialist, and its purpose is to explain to the child what he is to expect when admitted for a tonsillectomy. It is illustrated with drawings by James Bama. The text itself, unfortunately, "writes down" to the child and is appropriate only for very young children. It does not measure up to several texts of a similar nature which are available for the same purpose and are broader in scope.

La puberté. Étude clinique et physiopathologique. Edited by Guy Laroche, Paris, 1956, Masson & Cie, 394 pages. Price 2,800 francs (Fr.).

This is an entirely new revision rather than a second edition of a text published a number of years ago. It contains several interesting discussions of various phases of puberty, and a dozen authorities have contributed to the text. The topics range from the mechanisms of puberty, by Simonnet, which presents the part played by various organs and hormones, to the psychological and psychopathological aspects of puberty, by Assailly. Those who are interested in this age period and who can read French will find the book worth reading. Most of the authors show an extensive knowledge of worldwide literature.

The Treatment of Burns. Curtis P. Artz, M.D., and Eric Reiss, M.D., Philadelphia, 1957, W. B. Saunders Co., 250 pages.

The senior author was formerly the director of the Surgical Research Unit at the Brooke Army Medical Center, and the monograph is based on the treatment and investigation of over a thousand patients with burns admitted to the Brooke Army Hospital. After a discussion of the scope of the burn problem, the initial treatment is taken up: first aid and appraisals, initial replacement therapy, and local care. Other chapters take up in detail the problems of infection, metabolic response, and nutrition, burns of specific areas, and skin grafting. A final chapter discusses the management of burns in disaster. Burns are a major cause of hospitalization. In 1954 there were 6,800 deaths from burns in the United States, and it is estimated that there were 70,000 admissions for burns. Much has been learned in regard to the treatment of burns in recent years. Children form about one half of the patients hospitalized because of burns, and at least half of the accidents could have been prevented. It is a well-written, important, practical monograph.

The Writing Road to Reading. Romalda B. Spalding with Walter T. Spalding, New York, 1957, William Morrow & Co., 238 pages. Price $4.00.

A detailed presentation of what the author terms the Unified Phonics Method for teaching children correct and accurate speech, writing, spelling, and reading. The author acknowledges her indebtedness to the late Dr. Samuel T. Orton. The subject of methods has been one of considerable controversy in recent years.

The Essentials of Paediatrics for Nurses. I. Kessel, M.B., M.R.C.P., Edinburgh, 1957, E. & S. Livingstone, Ltd. (Baltimore, Williams & Wilkins Co.), 213 pages. Price $4.75.

A brief manual on the diseases of infancy and childhood for use in nursing instruction. The author is Pediatrician to the Transvaal Memorial Hospital in Johannesburg. The book does not consider the nursing aspects. It will be of particular use to those who give pediatric lectures to nurses in training.

The Riddle of Stuttering. C. S. Bluemel, M.D., Danville, Ill., 1957, Interstate Publishing Co., 142 pages. Price $4.50.

Speech Correction at Home. Morris Val Jones, Ph.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 138 pages. Price $4.75.

Editor's Column

"THE TIMES HAVE CHANGED"

JUDGING by remarks, the "younger generation" of pediatricians were highly amused by the two examples of light verse by the late John Ruhräh which were included in his Profile by Wilburt Davison in the May issue of the JOURNAL.

It may interest them to know that the matter did not end with the verses entitled "The Times Have Changed," based on reading Joseph Brennemann's paper on child psychology. The cudgels were taken by L. J. B. (obviously a psychiatrist) in the "Tonics and Sedatives" column of the *J. A. M. A.* for March 10, 1934, and this brought forth a reply in the March 24 issue by R. S. (Ramsay Spillman).

Recalling how much fun the verses gave us twenty-odd years ago, the Editor dug them out of his files.

THE TIMES HAVE CHANGED

The times have changed, say John and Joe,
(Two noble men who ought to know).
Did children show some slight defection,
Their souls were saved by swift correction.
Did children shun their tasks or churching,
They promptly had a taste of birching.
Unknown the noisome verb: 'to pamper.'
Nor did those *angels* dare to hamper
The whims and wishes of their elders,
Who ranked supreme as conduct-welders.
And many were the lessons driven
By insight rigid and God-given.

The times have changed, and now some doctors
Presume to act as guides and proctors;
To comprehend the child's behavior,
And comprehending, act as savior;
To lean on wisdom, not emotion;
To cast aside the hollow notion
That children have the curse of Adam,
And should be crushed down like macadam.

Then will you tell us, John and Joe,
(We ask because you surely know),
Was whipping truly not a scandal?
Is chastisement a way to handle
An infant in the act of growing
Who needs, not punishment, but *showing?*
Who should not be denied expression,
Which often *does* create regression;
Who should not be shut by a stopper,
But should have help both *sane* and *proper.*
The times *have* changed, and, John and Joe,
Perhaps it is much better so.

L. J. B.

THE TIMES HAVE CHANGED

The times have changed, yes L. J. B.,
That's plain to you and plain to me;
To Ruhräh and to Brennemann,
In fact, it's plain to any man.

In T & S for March the tenth
I read your little piece at lenth.
I also read John's and I wot
I read Joe's too, but you did not.
For had you had the pains to read,
Ere sounding off with such a screed,
The piece by Dr. Brennemann
(Year, '33, the issue, Jan.),
You'd not incite this bard's guffaw
By having at a man of straw.
For when of "help both sane and proper"
You thusly speak, you come a cropper;
For Joe pleads, too, that folk be sane
And simply wishes they'd refrain

From giving o'er the helpless brat
To psychs who prate of this and that,
Who see in mother-love a hex
Based on the Oedipus complex—
Whose piercing analytic sight
Discerns in anything upright
As obelisk or post or tree
A symbolistic fallacy.
(No mother of the olden school
Was told "Shut up, you damned old fool!"
At least a child who pulled such stunts
Would never do it more than once.
Yet cracks like this, I grieve to say
Are very much in vogue today
In circles where the mothers shun
Inhibiting the little one.)

Oh, God of Reason. if Thou be,
Accept this little prayer from me:
Grant to this so-called Fem. hygiene
Which dominates the current scene.
Efficacy from night to morn
To save a race from being born
Into a world where Ph.D.'s
Forbid the touch of mother's knees.
Just let, I pray, the human race
Go by default and leave the place
Where man once ruled, to some new strain
Of being that may grow a brain
That can take life just in its stride
Without psychologists to guide.

R. S.